The Yale Journal of Biology and Medicine

SAMUEL CLARK HARVEY NUMBER

Vol. 23, No. 6 June, 1951 New Haven, Conn.

THE YALE JOURNAL OF BIOLOGY AND MEDICINE

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Entered as second-class matter January 11, 1929, at the post office at New Haven, Connecticut, under the Act of March 3, 1879.

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THE YALE JOURNAL
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SAMUEL CLARK HARVEY NUMBER

June, 1951

Volume 23 Number 6

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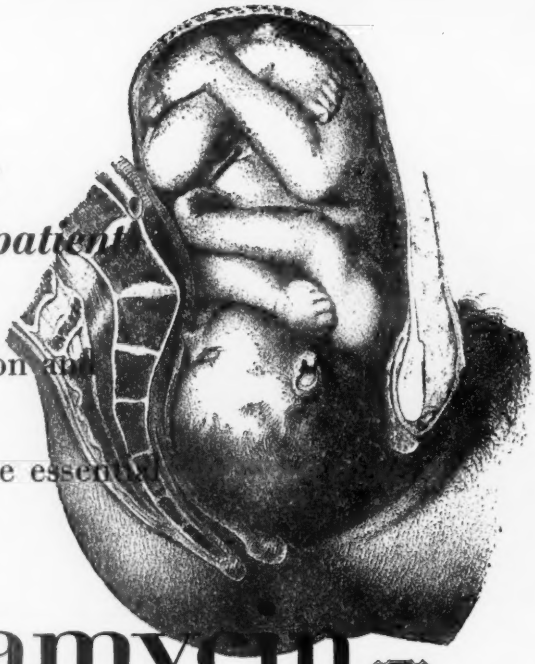
of an antibiotic
for obstetrical patient



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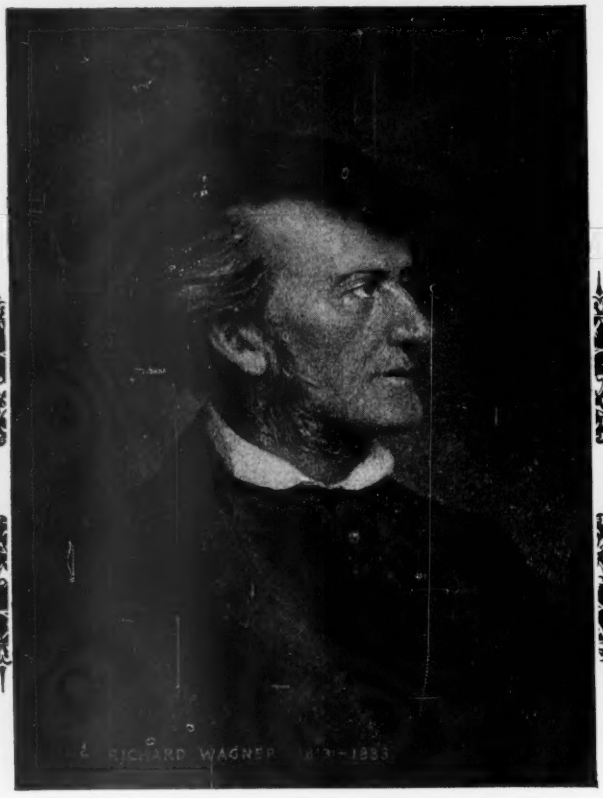

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SAMUEL CLARK HARVEY

SAM HARVEY
YANKEE SURGEON — PHILOSOPHER

GROVER F. POWERS

"The law of reserve is condemned to be broken down by the claims of the heart, and thus we all get into a position where we must step outside our aloofness, and to one of our fellow men become ourselves a man." Albert Schweitzer.

For apt terminology in characterizing the career of Sam Harvey, one turns to the profession of law; had he been a member of the bar his rôle would have been that of the scholarly judge primarily interested in the philosophy of the law, rather than that of a shrewd and showy trial lawyer. No field of knowledge is foreign to his interests and his erudition is apparent in even brief contacts; in medicine, his natural milieu is the laboratory and library, gifted though he is at the bed-side and in the operating room. A casual perusal of his *curriculum vitae* might lead one erroneously to a different appraisal; one notes the military career on the front-lines, the memberships on innumerable committees, the official positions in city, state, and national scientific organizations, the community and governmental activities of many and of diverse types; these would seem to characterize a busy man of affairs in medicine rather than the scholar and investigator. But it is just because of study and research and of wide reading, (a family joke was, "Sam is always reading!") by one with a retentive memory in socio-economic and historical fields as well as in all scientific areas, that the wisdom and experience come which bring request after request for counsel and guidance. Coupled with knowledge, experience, and wisdom, Dr. Harvey has a profound sense of responsibility for professional and public service. All of these attributes combine to take the scholar from the cloistered hearth and ivory tower into the forums of discussion and policy formulation.

But the productivity of the scholar is not lost, as is amply shown in his bibliography which demonstrates also the approach and interest of the philosopher in medicine. The studies in the healing of wounds and burns would in subject and content have delighted another sage and surgeon-philosopher—William Stewart Halsted.

Dr. Harvey has definite and strong convictions about education; these grow from personal experience as well as from observation. Emphasis is on learning, not teaching; one learns in proportion to what he puts of himself into the learning experience—not from listening to presentations, however skillful, of what someone else has learned. The great teacher functions, in

his opinion, by the example he sets in his daily activities in which he is himself a learner, a skeptic of established dogma, and a seeker of further knowledge. He spoke to me once in appreciative terms of Professor Leo F. Rettger as one of his great teachers. I asked him the basis for the tribute; said Dr. Harvey in substance: "He gave me a microscope and a laboratory, said he would be available if I needed him, and then left me to work out my own salvation."* This point of view is incisively expressed by Harvey in his address entitled "The Objectives of Medical Education."

> It will be asked, if the student be left to his own initiative for the acquisition of an adequate content of knowledge, can one be certain that he will do this? In the first place, it should be understood by faculty and student alike, that this is the student's responsibility. The faculty provides adequate opportunities, sympathetically advises, and outlines the paths along which the student must go, but *he* does the walking. It is no function of the faculty to provide him with transportation. The tuition is not carfare, but an entrance fee which covers only a small part of the costs of the caravan. It is to the student's interest primarily, rather than to that of the teacher, that he obtain an adequate medical education, and he should be disillusioned if he supposes that by the deposit of a fee he can transfer the weight of the burden to the faculty.

Fundamentally, this is the educational philosophy of the Yale University School of Medicine and no one regrets any deviation from the pattern more than Dr. Harvey; he believes consistent following of this educational philosophy will attract to the School students of the highest intellectual qualifications and will further its development as a true graduate school of medicine in contrast to a purely professional school of the usual type.

Dr. Harvey believes a fundamental and sustained knowledge of the sciences basic to clinical medicine is essential to the scholarly physician; he rendered more than lip service to this ideal—he has exemplified it in his

---

* Dr. Rettger tells the story as follows:

"One morning, I received a call in Old Sheffield Hall from Mr. Harvey, a premedical student. Harvey carried a paper bag which he handed to me. I said, 'What is this?' I opened the bag and found it contained some dead chicks. Said Mr. Harvey, 'They came from my father's farm; I have examined them and isolated an organism which I should like to show you.' I examined Harvey's material and found that the organism (Salmonella pullorum) which he had isolated was the one I had shown in Indiana to be the cause of a devastating epidemic disease of chickens. I had lost the organism and I said to Harvey, 'Why do you not study this disease and determine whether or not it is widely disseminated in this country!' A classic paper by Harvey (his first) was the result confirming the discovery of the etiology of a widespread and deadly epidemic disease of poultry."

Doubtless the late Professor Lafayette B. Mendel could have told a similar story of premedical student Harvey's development of the quantitative determination of chlorides in the urine known as the Volhard-Harvey method which is essentially the one in use in clinical laboratories today. Harvey suggested the elimination of a laborious and time-consuming step in the Volhard procedure but Dr. Mendel was doubtful and was convinced only after the new Harvey modification was checked successfully against the old on known solutions.

Dr. Harvey venerates his principal teachers in the premedical sciences and in medicine—Leo F. Rettger, Lafayette B. Mendel, Yandell Henderson, Henry B. Ferris, Joseph Marshall Flint, and George Blumer.

own life experience. He carried on special work in pathology, bacteriology, and chemistry; upon graduation from the Sheffield Scientific School of Yale he was offered an instructorship in chemistry in the Albany Medical College (at a salary of $1200 per year!) He declined this offer, which at the time was most tempting, to study pathology under Professor William G. MacCallum at the College of Physicians and Surgeons in New York. Because of this continuing background in the basic sciences he could become and is in the truest sense a general surgeon—one who is competent in the multifaceted domain of operative therapy. Harvey was a pioneer in the development of what are now considered special domains—thoracic, neurological, and vascular surgery. He is a master craftsman in the operating room, at home in these various branches of surgery. His technique is precise and meticulous; pyrotechnics and gadgets are not substituted for simple skill and dexterity. Of his Chief, Max Taffel has said: "Although he has been a professor these many years, he has never ceased to be a student."

Consultations with Dr. Harvey on professional matters involving specific patients are always for me a unique and stimulating experience. He gives meticulous attention to every detail of the care of patients for whom he assumes ultimate personal responsibility. But for the patients of other physicians the technique is different; Dr. Harvey sits impassively behind his desk, quietly puffs his pipe, asks a sharp question now and then, makes an occasional barbed comment, and lo! with or without a brief summary by him the diagnosis or therapy is clarified or the root of the problem brought into sharp focus and its complexity resolved! I am sure that every resident in surgery under Dr. Harvey will corroborate my experiences, recalling vividly the many five o'clock sessions when, after the moil and toil of the day, the knotty problems were presented to the Chief for the clarification sure to come. Complications and errors in diagnosis, treatment, or management of patients on the surgical service are not easily forgotten or ignored—they are recorded by assistant residents (quite literally and appropriately) in the service "Black Book"; for discussion of these reports, a weekly staff meeting is held—not always an hilariously happy occasion!

All who know Sam Harvey are aware—often to their discomfiture—that a keen sense of humor is as characteristic of him as is his erudition. His wit is barbed and pungent and his humor often of the earthy type. Harvey greatly admired the late Governor of Connecticut, Wilbur Cross, and they resembled each other in their sly humor and love of shrewd Yankee jokes and stories.

Sam Harvey is soon to retire from the clinic and the operating room but he can never retire from the lives of those whose careers in medicine have been vitalized by his sparkling wit and broad scholarship, his exemplary craftsmanship, and his wise judgments. His counsel in formulating policies in the socio-economic as well as educational areas of medical statecraft will

be reflected in the course which his profession will take in the years to come. And thus will his influence continue in the future; for

> . . . whatever it is that fills
> Life up, and fills it full, it is not time.

Curriculum vitae

Samuel Clark Harvey was born on February 12, 1886 in Washington, Connecticut, son of Calvin Ferry and Ellen Sophia Clark Harvey. After preparing for college at Woodbury High School and at Mount Hermon School, he received the Ph.B. degree from Yale University in 1907, and in 1911, the M.D. degree. For a year he was Alonzo Clark Fellow in Pathology, and then for a year Instructor in Pathology at Columbia University. There followed a year as Assistant Resident Physician at Loomis Sanatorium, Loomis, New York. His training in surgery began while he served as House Officer at Peter Bent Brigham Hospital, 1914-15, as Arthur Tracy Cabot Fellow in Surgery, 1915-16, and as Assistant Resident Surgeon under Dr. Harvey Cushing, 1916-17.

On July 1, 1917, Dr. Harvey was to assume the duties of Instructor in Surgery at Yale and Resident Surgeon in New Haven Hospital, but in April of that year he was commissioned as First Lieutenant, M.R.C., and in May he went overseas with the Peter Bent Brigham Hospital Unit, the U.S. Army Base Hospital No. 5. Later he served with Evacuation Hospital No. 7 and with Mobile Hospitals 6 and 8, and thus took part in the treatment of men wounded in battle. Promoted to Captain on June 26, 1918 and to Major, January 21, 1919, he continued on active duty until June 19, 1919.

Upon his release from the Army, he took up the duties at Yale which had been planned two years previously. Having finished his residency, he served one year as an Assistant Professor and three years as Associate Professor of Surgery and Acting Chairman of the Department. In 1922 the University received funds for the William H. Carmalt Foundation and Dr. Harvey's title carried this designation until 1935. His promotion to Professor of Surgery and Chairman of the Department occurred in 1924. In 1935 his title was changed to William H. Carmalt Professor of Surgery and so continued until his resignation from the Chairmanship of the Department in 1947. He then became Professor of Surgery (Oncology) and began to devote his attention almost exclusively to problems in the teaching, investigation, and treatment of cancer. From 1924 to 1947 he served as Surgeon-in-Chief of the New Haven Hospital with which he is still connected as an Associate Surgeon.

In the twenty years between 1920 and 1950, he served as a member and often as chairman of the several committees of the School of Medicine, a total of eighty-seven separate yearly appointments to committees! One of

his earliest appointments was to the Committee on the Curriculum, a subject which has held his interest throughout the years; later appointments included membership on the Committee on the Library (1942-50; Chairman, 1942-47), and in the Atypical Growth Research Unit of which he was Chairman, 1948-49. From 1927 to 1937 Dr. Harvey was Chairman of the University Department of Clinical Medicine.

Western Reserve University conferred on him the degree of Doctor of Science in 1931, and the following year attempted unsuccessfully to persuade Dr. Harvey to accept the Professorship of Surgery there. Other honors include membership on the American Board of Surgeons, 1942-49; election to the Board of Governors of the American College of Surgeons, 1936; President, Society of Clinical Surgery, 1940; President, Connecticut State Medical Society, 1948; President, American Surgical Association, 1950; and recipient of the American Cancer Society Award, 1950. He is a member of the following organizations (in addition to those just noted): Society of University Surgeons; Society of Neurological Surgery; Association of Thoracic Surgery; Fellow, American Medical Association; American Surgical Association; New England Surgical Society; New England Cancer Society; A.A.A.S.; and a member of Sigma Xi. Since 1931 Dr. Harvey has been Consulting Surgeon, Connecticut State Tuberculosis Commission; and at the present time he is also occupied with the duties of Chairman, Connecticut Advisory Committee to Selective Service.

CONGENITAL CYSTIC DILATATION OF THE RENAL COLLECTING TUBULES

A New Disease Entity*

VINCENT VERMOOTEN**

In 1943, while I was in the U. S. Army, a young soldier was referred to me because of gross, painless, total hematuria and a peculiarly abnormal excretion urogram. Except for this gross abnormality which looked as though a bunch of grapes were attached to each minor calyx (Fig. 1a and 1b), no explanation could be found for his hematuria. There was no evidence of calculous disease. There was no pus in his urine. All renal function tests were normal. All blood studies were within normal limits. After retrograde pyelographic study had been repeated twice and excretion urographic studies three times, one could draw no conclusion other than that this man had gross, cystic dilatation of the collecting tubules of both kidneys. It was a condition, which, as far as I could find out, had not yet been described in urological literature.†

In reviewing seven hundred complete urographic studies made in my recent private practice, I found that 236 retrograde pyelograms were made and 464 excretion urograms. Of these, 86 patients had had both excretion and retrograde studies.

In re-examining the urograms carefully, paying particular attention to the minor calyces, it was found that 52 had to be discarded as the visualization was too poor to see clear-cut minor calyces. Of the remaining 648, visualization was sufficiently adequate to get a good picture of most of the minor calyces. In studying these, I was not surprised to find that the collecting tubules could be visualized in 35, or just over five per cent of the total. In eleven, this was just a faint fan-like area of radio density. In thirteen, it was more marked and here one could see a certain degree of beading along the lines which radiated out from the calyx. In the remaining eleven, the visualization of the collecting tubules would be apparent to even the most casual observer. It is apparent, therefore, that the collecting

* From the Department of Urology, Southwestern Medical School, University of Texas, Dallas, Texas.

** Assistant Resident Surgeon, New Haven Hospital, 1925-1927.

† Since preparing this manuscript, I have had a communication from Doctor Wyland Leadbetter, through the Urologists' Letter Club, reporting that he has seen this lesion five times in the past twelve years. He has also found a report in the J. urol. méd., Par., 1949, *55*, 498, by Robert Cacchi and Vincenzo Ricci, entitled "Sur une rare maladie kystique multiple des pyramides rénales le 'rein en eponge,'" in which the authors report five instances of this lesion. These additional observations confirm my impression that this lesion is not as uncommon as one would be led to believe by the almost complete absence of any reference to it in the literature.

Received for publication April 18, 1951.

tubules can be visualized in a small percentage of individuals, especially by excretion urography, provided the patient has been adequately prepared for this study. As a rule, visualization is best in the film exposed twenty minutes after the intravenous injection of the radio-opaque medium. This picture must not be confused with Hinman's "pyelo-venous backflow" which is at times demonstrated during retrograde pyelography.

It seems logical to me, therefore, that if an opaque organic iodide can be given intravenously and excreted by the kidney in sufficient concentration that the kidney pelvis, infundibula, and calyces can be sharply outlined, then the visualization of the collecting tubules in only a small percentage of instances would indicate that these tubules are dilated, and that the opaque medium is collecting in them as well as in the larger collecting system. In other words, there may be stasis in these collecting tubules. If that was true, one should expect, in favorable circumstances, that stones will form in these dilated collecting tubules, which will give the picture of "nephrocalcinosis." In my patient described above with the congenitally dilated, cystic collecting tubules, stones have subsequently formed, and now, eight years later, these are readily visualized on radiographic examination (Fig. 2a and 2b).

If one considers stone formation to be an advanced stage of this lesion, it will appear that the early stage of the lesion is not as uncommon as the near absence of any reference to it in the literature would indicate.

The minimal manifestation of this condition appears as a thin-veiled filling of a minor calyx with a soft brush-like end (Fig. 3). This is sometimes difficult to differentiate from a minor calyx seen in three-quarter view. When the renal collecting tubules are more dilated, one can see a fan-like projection extending out from the minor calyx. Frequently, one can see fine lines radiating out into the kidney, and often they are "beaded," suggesting the presence of multiple, small, cystic dilatations (Fig. 4a and 4b). These fan-like areas of radio-opacity vary in intensity and extent. Most commonly they are bilateral and not infrequently they involve all the renal pyramids, indicating that it is a generalized process involving most, if not all, the collecting tubules.

Figure 5 shows the lesion so well defined and obvious that it can hardly be missed by even a casual observer of X-rays. The flat plate of the abdomen revealed no evidence of calcification in either kidney area. I am unable to interpret the fan-shaped areas of increased radio opacity in the region of each renal papilla as anything but due to the presence of the excreted opaque iodide in cystic, dilated collecting tubules.

If the X-ray medium is so well concentrated in these collecting tubules that it can be seen in the radiograph, it stands to reason that urine is also well concentrated here. Flocks[1] has pointed out that there is considerably more calcium in the urine obtained from a kidney in which there is stasis than in the opposite kidney in which no stasis is present. That being the

case, one would expect calculi to form in these cystic, dilated collecting tubules, and, as we all know, they do. It has been a general feeling that stones form in the terminal collecting tubules and dilatation subsequently occurs. That this is possible but not always so is evidenced by the follow-up on my first patient. Here, calculi became manifest only four or five years after I had discovered this very advanced lesion of cystic dilatation of the renal collecting tubules.[2]

When once, as a result of stasis, infection sets in or stones form, one would expect that the dilatation will progress more rapidly. That this is the case is particularly well illustrated in a 60-year-old man who had an excretion urogram made as a routine preprostatectomy study. His flat plate revealed a few scattered tubule calculi (Fig. 6), but the excretion urograms showed very extensive pooling of the radio opaque medium in all the pyramids (Fig. 7). It is apparent that these calculi have contributed to a certain extent to the extensive dilatation of the collecting tubules which must have been present before the formation of the calculi, but they cannot possibly account for all the dilatation.

In contrast to this, we see a 54-year-old white male with very extensive nephrocalcinosis without hyperparathyroidism and with a minimum of obviously dilated collecting tubules (Fig 8a and 8b). This patient, who subsequently died from carcinoma of the stomach, also had an extensive, old, chronic pyelonephritis. It is possible that the scarring and contracture secondary to the infection may have prevented the usual pooling of the opaque iodide in these areas.

In the above series of urograms there was one showing several single "cysts" in the collecting tubules in the upper pyramid on the right, but no evidence was seen of cystic dilatation of the other collecting tubules (Fig. 9). There were also five instances in which there was a solitary, localized cystic dilatation of one of the collecting tubules. In three, calculi had formed, and in two no calculi were present. In one instance this lesion was bilateral (Fig. 10a and 10b). These "calyceal diverticula," as they have been called, are better visualized on excretion urography than by retrograde study—exactly as are the generalized cystic dilatations of the collecting tubules. I feel that these solitary, or multiple, large cysts of the collecting tubules (calyceal diverticula) are a manifestation of the same process that we are discussing. They are in the correct location and they fill and empty exactly as do the cystic, congenitally dilated tubules. That these dilated collecting tubules can be, at least partially, filled on retrograde injection is seen in my patient with this very extensive lesion and no calculi, as well as in the one with the innumerable tubule calculi. Only in rare instances and only when the process is far advanced does this take place, for with the exception of these two cases this was not seen in any other of my 236 retrograde pyelographic studies.

FIG. 1a. (Right kidney): Excretion urogram showing extensive areas of opaque media given intravenously appearing in what apparently must be considered as cystic areas of dilatation involving all the collecting tubules of both kidneys.

FIG. 1b. (Left kidney): Excretion urogram showing extensive areas of opaque media given intravenously appearing in what apparently must be considered as cystic areas of dilatation involving all the collecting tubules of both kidneys.

FIG. 2a. (Right kidney): Plain radiograph taken eight years later of the same patient described in Fig. 1, now showing multiple small calculi forming within dilated tubules.

FIG. 2b. (Left kidney): Plain radiograph taken eight years later of the same patient described in Fig. 1, now showing multiple small calculi forming within dilated tubules.

FIG. 3. Excretion urogram on a thirty-six-year-old woman who was seen because of urethral symptoms. There was no infection present. Excretion urogram shows the early lesion of congenital cystic dilatation of the collecting tubules. Note the fan-shaped areas extending out of the calyces with brush-like ends.

FIG. 4a. (Right kidney): Excretion urogram of a thirty-two-year-old woman who was seen on account of frequency of urination. There was no infection or symptoms referable to the kidney. Routine excretion urogram reveals again fan-like areas of increased density with delicate brush-like ends extending into each pyramid from minor calyx. Note the beading along the radiating lines indicating early cystic dilatation of the collecting tubules.

FIG. 4b. (Left kidney): Excretion urogram of a thirty-two-year-old woman who was seen on account of frequency of urination. There was no infection or symptoms referable to the kidney. Routine excretion urogram reveals again fan-like areas of increased density with delicate brush-like ends extending into each pyramid from minor calyx. Note the beading along the radiating lines indicating early cystic dilatation of the collecting tubules.

FIG. 5. Extensive areas of radio-opacity extending out from each minor calyx is obvious to the most casual observer. This indicates dilatation of all the collecting tubules involving most of the pyramids.

FIG. 6. Scattered small, rounded calcific deposits seen throughout the left renal area of this sixty-year-old patient.

FIG. 7. Excretion urogram made on the patient described in Fig. 6. Note the multiple, cystic, dilated areas involving practically all the collecting tubules. An occasional cyst contains a stone. There are some areas of pooling of the opaque medium involving the entire pyramid. The lesion in this instance is almost as advanced as that shown in Fig. 1. The pyelogram of the right kidney is similar to this one.

FIG. 8a. Plain radiograph of the right kidney of a fifty-four-year-old man. Note the extensive deposition of individual small calculi involving all the pyramids.

FIG. 8b. Excretion urogram made on the patient whose flat plate is shown in Fig. 8a. Notice how the opaque medium is being deposited in all the areas where the calculi are, suggesting that the calculi formed in these cystic areas, for there is no indication that there is any obstruction.

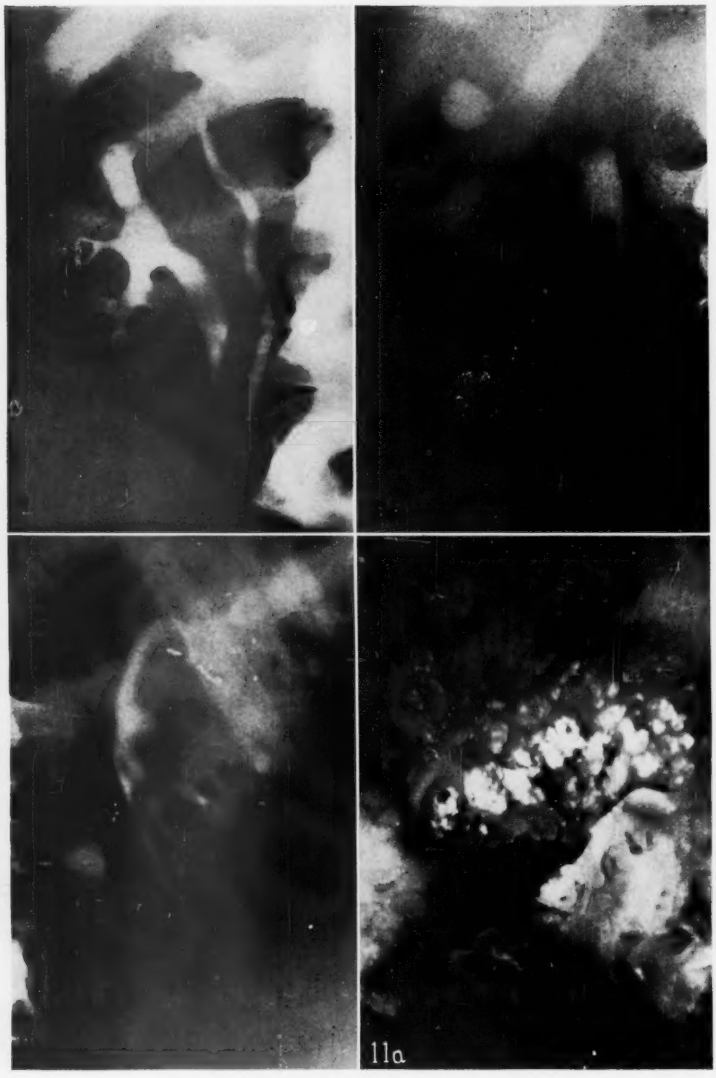

FIG. 9. Excretion urogram showing several large solitary cysts in the collecting tubules just outside the upper calyces of the lower kidney. Note also the early fan-shaped areas extending out from the calyces of the lower pole of the kidney.

FIG. 10a. Solitary cyst visualized as being attached to the upper minor calyx.

FIG. 10b. Radiograph of the left kidney of the same patient showing small, individual cysts on the collecting tubules. The one attached to the middle calyx system is very well visualized.

FIG. 11a. Close-up of a renal pyramid of the specimen shown in Fig. 11b. Great masses of uric acid crystals are seen in the terminal collecting tubules, although it would appear that there is some deposit of uric acid even higher up. Had this individual lived, his pyelogram might have very readily resembled the one shown in Fig. 1.

FIG. 11b. Gross photograph of a kidney removed from a fetus near term. Note the massive deposits of uric acid crystals in practically every pyramid.

Etiology

In 1937, shortly after Doctor Alexander Randall published his first paper on the occurrence of calcific plaques upon renal papillae, I had the opportunity of studying over two thousand pairs of kidneys in the Police Medicolegal Laboratories in Johannesburg, South Africa. In this study I frequently found the pelvis of premature or term fetuses full of uric acid crystals which appeared as fine, crystalline sand. Less frequently these fine uric acid crystals were also seen, with a magnifying glass, in the renal pyramids, presumably in the collecting tubules. In no less than three instances I found the renal pyramids solidly packed with great masses of uric acid crystals—the so-called uric acid infarcts (Fig. 11a and 11b).

It is well known that uric acid is from ten to twenty times more soluble in urine than in water, and that urine is "formed" (concentrated) in the collecting tubules. It must also be remembered that the kidney is a functioning excretory organ in fetal life. With these facts in mind, one should not be surprised, therefore, to find uric acid crystals in the renal pelves of full- or near-term fetuses, and, at infrequent times, massive "uric acid infarcts."

After birth, when the kidneys are on their own, it seems reasonable and logical that the uric acid should be dissolved and excreted. It also seems reasonable to assume that a varying degree of permanent damage to the collecting tubules may have resulted, especially secondary to "uric acid infarcts."

I would, therefore, like to propose a theory that "congenital dilatation of the collecting tubules," cystic or otherwise, is the end result of the damage done to the collecting tubules by the deposition of uric acid crystals in these tubules during fetal life. The faint, fan-like visualization of the collecting tubules is the minimal lesion, and my first case described in this article the maximal lesion consistent with life. "Calyceal diverticula" appear to be localized lesions of this type, while "nephrocalcinosis" is actually multiple tubule calculi which have formed in these congenitally dilated collecting tubules irrespective of the cause of the hypercalcinuria.

Summary

A new disease entity, "congenital dilatation of the renal collecting tubules," is described.

A theory is offered as to its origin and development.

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CORTISONE AND HOMOLOGOUS TRANSPLANTATIONS OF TUMORS*

EDWARD L. HOWES**

Cortisone retards the initiation of mesenchymal reaction after injury.[1] We have shown that new capillaries do not proliferate, that reticulin is not elaborated, and that the fibroblasts seem supressed. On the other hand, epithelization occurs, although its rate is somewhat slowed. These changes occur regardless of whether cortisone is administered generally or locally.

Transplantation of tumors succeeds if the "stromal reaction" occurs and the transplanted tissue is able to acquire a new blood supply. This stromal reaction is a mesenchymal proliferation and likewise should be repressed by cortisone. It has been studied by many and has been summarized by Woglom,[8] as follows:

> The first evidence of reaction to the graft was a rapid aggregation of polymorphonuclear leucocytes in the surrounding tissues of the host, beginning about two hours after the introduction of the tumor fragment and of short duration only. The leucocytes collected about any necrotic material present and even penetrated between the tumor cells. About fifteen hours after the introduction of the graft there occurred proliferative changes in surrounding areolar connective tissue of the host, the cells of which became shorter and thicker, while their nuclei divided by amitosis. The proliferating cells migrated into the cleft which originally separated the connective tissue of the host from the newly introduced fragment, and applied themselves to the surface of the graft. The stroma had already become hyaline after twenty-four hours, and commencing degeneration could often be detected in its cells. Such changes were even more distinct after thirty-six hours. . . . The capillaries of the graft with their blood corpuscles were still recognizable, although the endothelium showed degenerative changes. Outside of the graft fibrin filaments had appeared in the exudate and amitotic division of the connective tissue cells was still in progress, while spindle-shaped wandering cells had begun to penetrate the transplanted tumor. Three days after inoculation the cleft between the tumor and the host's tissues was almost obliterated, and wandering cells could be distinguished in the interstices of the graft, where they were dividing by mitosis. Mitotic division was in evidence, also, in the fibroblasts of the host nearest the tumor. . . . No development of new blood vessels had yet occurred and the whole mass of transplanted tissue remained without vascular supply. Four days after transplantation, however, an ingrowth of capillaries had taken place and vascularization was in such rapid progress that all stages of new capillary

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Received for publication April 24, 1951.

formation might be found in the same specimen. Fibroblasts from the host were streaming into the tumor from every side, some of them appearing to exercise a phagocytic function and finally to degenerate, while others survived to form the new stroma. The old connective tissue still remained, but was in the last stages of degeneration. From four days onward there was a continual recession of the stroma originally introduced, and an orderly progress of vascularization until, by the eleventh day, fibrils of new-formed collagen could be found in the new stroma which, at the eighth, had been very cellular.

If cortisone retards the stromal reaction, theoretically even autogenous transplantations should be less successful under the influence of cortisone.

On the other hand, certain evidence suggests that the failure of homologous transplantation may be caused by an immune reaction that is partially responsible for the absorption of the transferred tissue, and cortisone suppresses allergic immune reactions.[5] The following table showing the principal changes that occur when the graft does and does not take indicates the rôle of the immune reactions in unsuccessful homologous transplantations.

INTERACTION BETWEEN TISSUES WHEN TRANSPLANTATION IS SUCCESSFUL AND UNSUCCESSFUL

(Modified after Loeb[2])

	Autotransplantation Successful	*Homologous transplantation Unsuccessful*
First Phase	Reaction dominated by injury due to transplantation. Survival of cells.	Reaction dominated by injury due to transplantation. Survival of cells.
Second Phase	Capillary invasion to nourish graft. Growth of graft.	Accumulation of lymphocytes. Capillaries do not invade. Partial necrosis of graft. Graft fails to grow.
Third Phase	Established new blood supply. Growth continues.	Complete destruction of graft. Some encapsulation of area.

Also, in some unsuccessful transplantations the tumor starts to grow in the second phase for a day or two and then suddenly necroses, suggesting an increase of some circulating immune substances in the host that are toxic to the cells of the tumor. In addition, cortisone can apparently reduce the number and change the activity of some of the mononuclear phagocytic cells, possibly including the lymphocytes that appear about unsuccessful homologous transplants. For example, Spain, Molomut, and Haber[4] found that cortisone-treated animals did not have enlarged lymph glands filled with particles after injection of carbon into the peritoneal cavity. Instead, the particles were spread out and the lymph nodes were barely visible.

Theoretically, then, with the diminution of the awareness of the host tissues, the transplant should be able to grow more successfully under the influence of cortisone, particularly if it were composed of epithelial cells with a high growth potential.

To determine whether cortisone will aid or hinder the transplantation of tumors, the following investigation was carried out. Whitelaw[7] believes that he has grafted normal skin homologously under the influence of ACTH. The one clinical trial cited is undocumented and uncontrolled. Sugiura, Stock, Dobriner, and Rhoads have tested the influence of cortisone on growth of tumors already transplanted.[8]

Methods

Two methods were employed to test the influence of cortisone on homologously transplanted tumors. In the first method, cortisone was given to the Rockland Swiss white mice that are relatively resistant to the transplantation of tumors E0771 and 775. These adenocarcinomata are usually transplanted and grow successfully in the C57 black mice. Cortisone was given parenterally to the white mice in doses varying from 0.005 mg./gm. to 0.01 mg./gm. starting two days before to ten days after transplantation of the tumors from the black mice. With both tumors cortisone was also implanted locally at the time of transplantation. Semi-solid cortisone was obtained by centrifuging its suspension, and a very small amount was placed on the transplant by dipping the end of a probe into the residue and wiping it on the transplant. In the first experiments, one transplant was placed on each side of the abdomen of one mouse and both tumors were treated with cortisone. Later, only one transplant was treated in each animal, keeping the other side for a control. Special care was employed to be certain that cortisone did not contaminate the instruments used to transplant the untreated tumor.

In the second method, tumors were produced in white Wistar rats by means of methylcholanthrene incorporated in transplanted stomach mucosa. Most of these tumors took a year or more to develop. When they were first transplanted in the Wistar rats, half of the rats were treated with cortisone while the other half were not. The type of tumor transplanted is indicated in Table 3 as well as the information indicating whether the transplantation was the initial or the second sub-transplantation. Cortisone was given parenterally, 30 mg./kg., to some of these animals while it was implanted locally with the tumor in others.

With both methods, the tumor growths were measured on the seventh, ninth, and fourteenth days. Gross examination was made of all tumors to observe the extent of necrosis and the degree of encapsulation. Sections were taken from each tumor for microscopic examination.

The mice and rats were fed on a standard laboratory diet before and throughout the experiment. Some initial testing had to be done to find the dose of cortisone that would not kill the animal and yet be large enough to disturb allergenic reactions and the regeneration of the mesenchyme.

Results

Cortisone, given parenterally and implanted locally, definitely increased the number of successful homologous transplantations of the adenocarcinomata transferred to a new strain of animals in which they ordinarily did not take. The percentage increase of successful takes was greater for tumor EO771, which normally showed a higher incidence of success with homo-

logous transplantation, than for tumor 755 (Table 1 and 2). Tumor 755, with an incidence of only 2.8% positive homologous transplantations, increased under the influence of parenterally administered cortisone to 33%, while EO771, which originally gave 33% positive homologous transplants, rose to 95% positive transplants under the influence of parenterally adminis-

TABLE 1

TRANSPLANTATION OF E0771 TUMORS IN MALE MICE

Transplantation without cortisone		*Transplantation with cortisone*	
		*Parenteral. O.D.**	*Local*
C57 mice	*Rockland Swiss*	*Rockland Swiss*	*Rockland Swiss*
14 days' duration 8 positive 0 negative	17-26 days' duration 2 positive (limited growth) 6 negative	8-26 days' duration 0.01 mg./gm. 5 positive 0 negative	14 days' duration 7 positive 3 negative (different animals)
14 days' duration 7 positive 1 negative	17-26 days' duration 4 positive (2-limited growth) 6 negative	26 days' duration 9 positive (large tumors) 0 negative 0.005 mg./gm. 3 days before 0.01 after tpl. 14-16 days' duration 4 positive (large tumors) 1 negative 0.005 mg./gm.	14 days' duration 8 positive 2 negative (same animal)
15 positive 1 negative	6 positive 12 negative	18 positive 1 negative	15 positive 5 negative
94% positive	33% positive	95% positive	75% positive

* Two days before to 10 days after transplantation.

tered cortisone. Local cortisone increased the number of successful homologous transplants to 80% for the 755 tumor and to 75% for the EO771 tumor.

Parenterally administered cortisone doubled the number of successful homologous transplantations of methylcholanthrene-induced tumors in the rat even though they were largely of mesenchymal origin. These induced tumors took in 56% of the rats given cortisone, whereas only 11% took when no cortisone was given (Table 3).

In a smaller group of rats, the transfer of methylcholanthrene-induced tumors was made from August Tan and White rats to Wistars. For this group, the incidence of successful transplants rose in the Wistars from 0 to

TABLE 2

TRANSPLANTATION OF 755 TUMORS IN MALE MICE

Transplantation without cortisone		*Transplantation with cortisone*	
		*Parenteral. O.D.**	*Local*
C57 mice	*Rockland Swiss*	*Rockland Swiss*	*Rockland Swiss*
16-23 days' duration 9 positive 1 negative	26-30 days' duration 0 positive 8 negative	3-8 days' duration 0.83 mg./gm. all mice died 3-8 days one died 8 days with tumor	14 days' duration 10 implants in 5 mice 8 positive 2 negative (different mice)
17-30 days' duration 9 positive 1 negative	30 days' duration 0 positive 5 negative	14-30 days' duration 0.01 mg./gm. 3 positive 5 negative	
	26 days' duration 0 positive 10 negative	23-30 days' duration 0.005 mg./gm. 1 positive 4 negative	
	17-31 days' duration 0 positive 5 negative	14-17 days' duration 0.005 mg./gm. 3 positive 5 negative	
	16-28 days' duration 1 positive 6 negative		
18 positive 2 negative	1 positive 34 negative	7 positive 14 negative	8 positive 2 negative
90% positive	2.8% positive	33% positive	80% positive

* Two days before to 10 days after transplantation.

22% under the influence of cortisone (Table 4). Eighty per cent of the transplants took when the inbred strain of August Tan and White rats was used for the first transplantation when no cortisone was used. This figure is much higher than for the commercial Wistar to Wistar transplantation without cortisone; with these only 11% took.

All transplants growing under the influence of cortisone grew poorly as compared to those growing in the susceptible hosts.

Gross and microscopic examination showed that the EO771 and 775 tumors, successfully transplanted into the Swiss mice under the influence of cortisone, developed a new blood supply. Grossly, many blood vessels, particularly veins, were seen over the surface of the tumors. Microscopically, the blood supply seemed to be more at the periphery of the tumor than

TABLE 3

METHYLCHOLANTHRENE-INDUCED TUMORS
WISTAR RATS TO WISTAR RATS (COMMERCIAL)

	With cortisone			*Without cortisone*				
Rat no.	*No. of rats*	*Positive*	*Negative*	*No. of rats*	*Positive*	*Negative*	*No. of injections*	*Microscopic diagnosis*
209/1A	2	2	0	2	0	2	26	Fibrosarcoma
228/1A	2	1	1	2	2	0	12	Fibrosarcoma
297/1A	3	3	0	3	0	3	7	Mesenchyoma undiff.
302/1A	3	1	2	3	0	3	7	Rhabdomyosarcoma & fibrosarcoma
302/2A	2	1	1	2	0	2	8	Rhabdomyosarcoma & fibrosarcoma
291/1A	3	0	3	3	0	3	8	Sarcoma
301/1A	3	2	1	3	0	3	8	Sarcoma
Totals	18	10	8	18	2	16		
Percentage		56	44		11	89		

when they were successfully transplanted in C57 mice. Lymphocytes were found in large numbers about EO771 tumors that were successfully transplanted but contained considerable necrotic tissue.

Discussion

No statistical analysis has been made of the results, for it is realized that the ultimate answer about the influence of cortisone on the transplantation of tumors can only be had by transferring many types of tumors in different animals. The results will certainly be affected by the cell composition of the tumors, the difference in susceptibility of the species to cortisone, and the capacity of the tumor for homologous transplantation before cortisone is given. The work suggests that cortisone enhances the tendency for homologous transplantation when the host is not too resistant.

Apparently, the stromal reaction was not inhibited by the presence of cortisone. Lymph nodes and lymphocytes were seen but they were more abundant in the 755 tumors where the percentage of successful transplants was smaller.

It is surprising that cortisone increased the number of successful transplantations of methylcholanthrene-induced tumors, largely of mesenchymal origin. Our previous experiments showed[1] that cortisone inhibits the initiation of mesenchymal proliferation, while the growth of fibrosarcomas, clinically, has not been arrested by the administration of cortisone.[2] However, experimentally, inhibition of growth depended on the type of tumor; some sarcomas were affected, others were not.[3]

TABLE 4

METHYLCHOLANTHRENE-INDUCED TUMORS
AUGUST TAN AND WHITE RATS

	To Wistar rats						*To Aug. T&W rats*				
	With cortisone			*Without cortisone*			*Without cortisone*				
Aug. T&W rat	*No.*	*Pos.*	*Neg.*	*No.*	*Pos.*	*Neg.*	*No.*	*Pos.*	*Neg.*	*Treatment*	*Microscopic diagnosis*
264/1A	3	1	2	3	0	3	3	3	0	Local	Sarcoma
263/4A	3	0	3	3	0	3	..	..	..	General	Spindle cell sarcoma
260/2A	3	1	2	3	0	3	2	1	1	General	Sarcoma
Totals	9	2	7	9	0	9	5	4	1		
Percentages		22	78		0	100		80	20		

Diminution of awareness of the host to the presence of the growth of a slightly foreign cell seems to be the best answer for the increased yield of homologous tumor transplants. The employment of cortisone ought to be useful to propagate the tumors needed in the study of cancer chemotherapy.

Conclusions

Parenteral administration of cortisone seems to improve the possibility of homologous transplantation of tumors, particularly if the tumor shows some tendency toward homologous transplantation. Diminution of awareness of the host is offered as a possible explanation.

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THE NITROUS OXIDE METHOD FOR MEASUREMENT OF CEREBRAL BLOOD FLOW AND CEREBRAL GASEOUS METABOLISM IN DOGS*

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Quantitative estimation of cerebral blood flow has been made possible by the recent introduction of the nitrous oxide method of Kety and Schmidt[7] and the dye method of Gibbs.[4] These indirect methods are particularly suited to the dog. The fallibility of direct methods and anatomical peculiarities of the dog have been discussed in detail elsewhere.[10] A corollary to the measurement of cerebral blood flow is the measurement of cerebral gaseous metabolism. This will be considered more fully later.

The following investigation was undertaken in the course of experiments devised to determine the effect of intracranial injury upon both cerebral blood flow and cerebral gaseous metabolism.[5] The present paper provides the technical background to this study, and also gives in detail the control observations made prior to intracranial injury.

The nitrous oxide method was used in preference to the dye method as the former had been published in more detail, had been applied to more varied situations, and sources of error had been better evaluated. The details of the technique are as nearly as possible those employed by Kety and Schmidt,[7, 8, 10] although they have not published the minutiae as applied to the dog. A few modifications which do not alter the validity of the method were made.†

General principles

The theory of the nitrous oxide method for determination of the cerebral blood flow has been described by Kety and Schmidt[7] and subjected to critical analysis, more recently by Kety.[9] In brief, it depends upon the fact that this gas is physiologically inert in the low concentrations employed.

Samples of blood are withdrawn simultaneously from the arterial and cerebral venous circulation at intervals after the animal begins breathing the gas. The levels of nitrous oxide measured in these samples are plotted against the time of their withdrawal. An arterial and venous curve of nitrous oxide content can be interpolated and the area between these curves

* From the Department of Surgery, Yale University School of Medicine. This study was aided in part by the grant provided by the Committee on Funds and Fellowships of Yale University School of Medicine. Presented in part at the 72d annual meeting of the American Neurological Association, June 17, 1947.

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† The authors are immeasurably indebted to both Drs. Schmidt and Kety for the advice which they gave unstintingly throughout this study.

Received for publication April 17, 1951.

is a function of the cerebral blood flow during the time of sampling. This relation may be expressed by the equation:

$$CBF = \frac{100\ V_t \quad S}{\int_0^t (A - V)\ dt}$$

where CBF is cerebral blood flow, as cc./100 gm. of brain/min.; V_t is the nitrous oxide content of the cerebral venous blood in volumes per cent when it is in equilibrium with brain tissue; S is the distribution ratio of nitrous oxide between blood and brain; $\int_0^t (A - V)\ dt$ is the integral of the arteriovenous difference of nitrous oxide in volumes per cent from the onset of nitrous oxide inhalation, 0, to equilibrium time, t. Equilibrium time is approximately 10 minutes, when the distribution of nitrous oxide between blood and brain is equal, hence S equals one.[20]

To supplement the determination of cerebral blood flow, an estimate is obtained of the average arteriovenous difference of oxygen and carbon dioxide during the period of the cerebral blood flow measurement. The necessary calculations depend upon the Fick principle. Applied to the cerebral circulation, this states that the cerebral oxygen consumption in cc. of oxygen is equal to the cerebral blood flow through the brain multiplied by the cubic centimeters of oxygen taken out of each cubic centimeter of this blood, or 100 CMR = CBF x $(A - V)_{O_2}$, where CMR is cerebral metabolic rate or the cerebral oxygen consumption.

Since $(A - V)_{O_2}$ is expressed in volumes per cent and CBF as cc./100 gm. min., the CMR is expressed as cc. of O_2/100 gm. of brain/min.

Method

The principal observations concerned cerebral blood flow and oxygen consumption in the lightly anesthetized dog. Subsidiary and often concomitant observations were made of other physiological functions. These included: pulse rate, respiratory rate, mean femoral arterial blood pressure, total body oxygen consumption, tidal air, respiratory minute volume, rectal, stomach, and skin temperatures. Room temperature was also recorded.

Material. Twenty-two mongrel dogs* of both sexes were operated upon in the morning after an evening fast (Table 3). Intravenous pentobarbital, 30 mgms./kg., supplemented when necessary by 5-15 mgm./kg. doses, was used to maintain relatively steady light anesthesia. The manipulations were made with a minimum of operative trauma and were unsterile.† Operative blood loss was not accurately determined

* Analysis of results in 17 experiments are presented.

† The temporal muscle was reflected prior to the first measurement in preparation for the observations to be made after intracranial injury.

though it possibly amounted to 25-100 cc. An additional 80 cc. of blood were required for each cerebral blood flow determination and ancillary measurements of oxygen and carbon dioxide. Large dogs between 10.8 and 26 kg. were used in order to avoid serious depletion of the circulating blood volume.

Technique of blood sampling. The mechanical arrangement of the apparatus is indicated in Figure 1A. Arterial blood was obtained from a cannula in a femoral artery. Cerebral venous blood was obtained through a cannula screwed into the

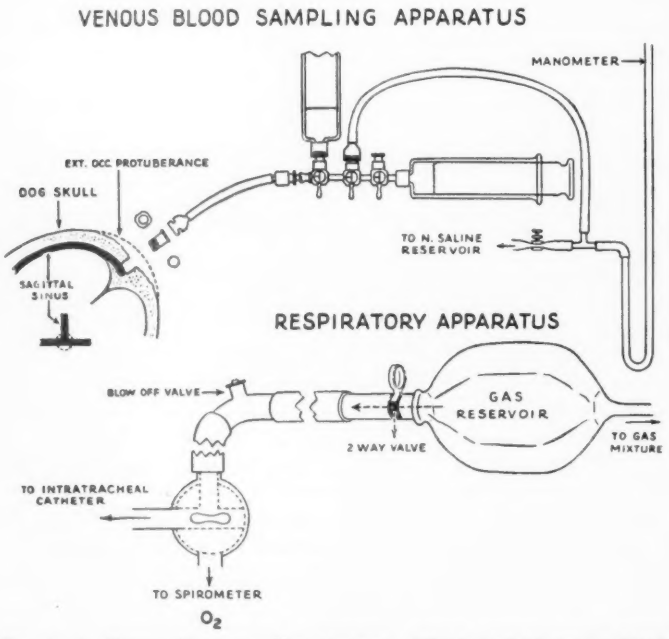

FIG. 1. A. Venous blood sampling apparatus. Mixed cerebral venous blood is obtained from the torcular as indicated. Arterial blood is obtained from the femoral artery with a slightly modified cannula for the artery and a Hg manometer. See text.
B. Respiratory apparatus. Nitrous oxide mixtures supplied from either a large spirometer, a closed system, or from the rubber-bag reservoir as indicated for an open system, provide the necessary inert blood gas. See text.

posterior portion of the skull in the midline, entering the sagittal sinus of the torcular. A series of three-way stopcocks was attached to the cannulae.

No systemic anticoagulant was used, although cannulae were rinsed with dilute heparin solution in normal saline or 5% chlorazole-pink.

Each sample of blood was between 3-5 cc. A few drops of 5% chlorazole-pink or heparin were used in 10 cc. syringes to prevent coagulation. The interior of each syringe was coated with mineral oil. Syringes filled with blood were capped with metal caps, shaken briskly and stored in ice and water. One cc. of mercury was added to each syringe after all samples were drawn.

A sample of arterial and one of venous blood were collected immediately before inhalation of the gas mixture was begun. After gas inhalation was begun, a series of five pairs of samples of arterial and venous blood were taken at 0-1 minutes, 1′ 15″, 3′, 5′, and 10′ respectively. Each of the last four samples was drawn in about 15″.

Technique of gas administration. The mechanical arrangement of the apparatus is indicated in Figure 1B. An intratracheal catheter with inflatable bag afforded a gas-tight airway. To this was attached a system of valves leading either to a gas mixture contained in a closed spirometer with soda-lime carbon dioxide adsorbent or to a rubber bag (an open system as indicated in Fig. 1B) which was filled with the gas mixture to be inhaled and also supplied with a blow-off valve for exhalation into the ambient air.

The closed system was used with a mixture of 25% nitrous oxide and 75% oxygen. Preliminary inhalation of 100% oxygen for about 30 minutes was needed partially to denitrogenate the blood to permit accurate analyses of nitrous oxide. The three-way valve, indicated, enabled immediate transition from breathing 100% oxygen provided in one spirometer to the gas mixture in a second spirometer. Both spirometers were fitted with soda-lime carbon dioxide adsorbent.

The alternate, open system, was more physiological. It required no preliminary denitrogenation or carbon dioxide adsorption, and used nitrous oxide and nitrogen mixed with 21% oxygen. Either 13% or 34% nitrous oxide was used.*

Technique of blood gas analysis. Blood gas analyses followed the techniques used by Kety, with the modification that 1 cc. volumes of blood were used instead of 2 cc. volumes satisfactory in man. The details not available are outlined.

When the simple nitrous oxide-oxygen mixture was used, the corrected partial pressure due to residual nitrogen in the preliminary sample was determined using factors for nitrogen as given by Van Slyke and Neil.[18] Then, the partial pressure of the nitrogen in the preliminary arterial sample was subtracted from the total inert gases in the other arterial samples and the partial pressure due to nitrogen of the preliminary venous sample was subtracted from the total inert gases in the other venous samples. These doubly corrected partial pressures were calculated as volumes per cent of nitrous oxide using the factors calculated by Orcutt and Waters.[19]

When a mixture of nitrous oxide, nitrogen, and oxygen was used, no preliminary inhalation oxygen was necessary and only a preliminary venous sample was needed. To eliminate the fraction due to nitrogen, Kety[7] has applied a correction which may be stated as follows: $V_{N_2O} = 1.03\ V_o - 1.1$ where V_o is the partial pressure of inert gases corrected for the partial pressure of reagents and water vapor (columns 7 and 8, Table 1).†

The manipulations used to determine nitrous oxide content described by Orcutt and Waters, and suggested in part by Kety, to expedite the analysis are as follows. For 1 cc. volume of blood: A standard Van Slyke-Neil apparatus was used to evacuate 7.5 cc. of distilled water and 2 drops of capryllic alcohol in the vacuum chamber at the 50 cc. level under mercury seal. After shaking for 1.5 minutes, 6 cc. of this emulsion were expelled into the cup above the chamber and used as a seal for the introduction of 1 cc. of whole blood into the chamber without contact with air. One cc. of emulsion in the cup was then reintroduced, washing the blood completely into the chamber. Two cc. of gas-free potassium hydroxide, hydrosulphite, anthraquinone beta-sulphonate solution were then added to adsorb all oxygen as well as carbon dioxide. A mercury seal was secured and the mixture was again evacuated at the 50 cc. level and shaken for

* Gas mixtures were obtained from the Thomas A. Edison Gas Co. of New Jersey.

† This has been recalculated for the percentages of gases employed and has been found to be unchanged.

3 minutes. A reading of the pressure of the evacuated gases and water vapor, P, (columns 2 and 3, Table 1) was obtained, and the temperature, tw, (column 1, Table 1) recorded as in example #15. Each observation, P, was also corrected for the partial pressure due to water vapor, $P_1 = P - P_{H_2O}$ (column 4, Table 1). Duplicate blank analyses, Pb, were made in exactly the same manner upon the reagents. Using a nomogram for convenience, the readings were corrected for the partial pressure of water at the temperature of observation, tw, e.g., $P_o = P_b - P_{H_2O}$. The corrected values were in turn corrected for the partial pressure due to the reagents in Pb, by

TABLE 1

DATA FROM GRAPH, EXPERIMENT #15

			$P_1 =$					*Time of drawing samples*		
t_W	S	P	$P-P_{H_2O}$	P_1-P_o	V_o	$1.03V_o$	V_{N_2O}	*Initial*	*Final*	*Mean*
°C.		*mm. Hg*			*vol. %*					
21.1	Pb	130.0	110.6	Blank on Reagents						
21.3	"	130.0	110.4	Mean 110.5 = P_o						
20.0	A1	172.3	154.8	44.3	11.81	12.18	11.1			
20.5	V1	142.0	123.9	13.4	3.57	3.68	2.6	0′ 30″	0′ 59″	.74′
20.6	A2	177.0	158.8	48.3	12.88	13.26	12.2			
21.0	V2	149.0	130.3	19.8	5.28	5.45	4.4	1′ 4″	1′ 16″	1.17′
21.3	A3	186.0	167.0	56.5	15.00	15.45	14.4			
21.3	V3	165.3	146.3	35.8	9.50	9.80	8.7	3′ 1″	3′ 9″	3.08′
21.0	A4	188.0	169.3	58.8	15.63	16.10	15.0			
21.0	V4	175.0	156.3	45.8	12.20	12.58	11.5	5′ 1″	5′ 10″	5.09′
21.0	A5	190.5	171.8	61.3	16.30	16.80	15.7			
21.0	V5	185.5	166.8	56.3	14.95	15.40	14.3	10′ 0″	10′ 10″	10.08′

Legend:
t_W Temperature of observation.
S Sample.
P Observed residual partial pressure.
P_{H_2O} Vapor pressure of water.
V_o Inert gas content of sample.
V_{N_2O} Nitrous oxide content of sample.

subtracting the mean P_o from all the observations, e.g., $P_1 - P_o$ (column 5, Table 1). These partial pressures, due to nitrous oxide alone, or nitrous oxide plus a small amount of nitrogen, were computed as content in volumes per cent with factors derived for nitrous oxide by Orcutt and Waters[12] (column 6, Table 1). A nomogram may be used here also for rapid calculation (Chart 1). Duplicate checks of nitrous oxide within 0.2 volumes per cent were consistently obtainable.

Calculations. The values of nitrous oxide content were plotted against the mid-time of drawing the samples. The area between the curves (Fig. 2) representing arterial and venous nitrous oxide content was determined graphically. The areas of trapezoids one minute in width and a length taken as the average ordinate in the period considered, were summed as illustrated in Figure 2 and Table 2. The area thus obtained was introduced into the equation for cerebral blood flow, together with the appropriate venous nitrous oxide content, and the cerebral blood flow computed.

The average arterio-venous oxygen and carbon dioxide differences during the course of the experiment were obtained by pooling simultaneous 5 cc. arterial and venous samples drawn before and after gas mixture inhalation. These were analysed in duplicate.

Nomograms for N_2O Content in Blood

$$pN_2O + pSol - P_b = pN_2O\,[pN_2O + pSol + pH_2O] - pH_2O = pN_2O + pSol \qquad pN_2O \times F = Vol\%\,N_2O$$

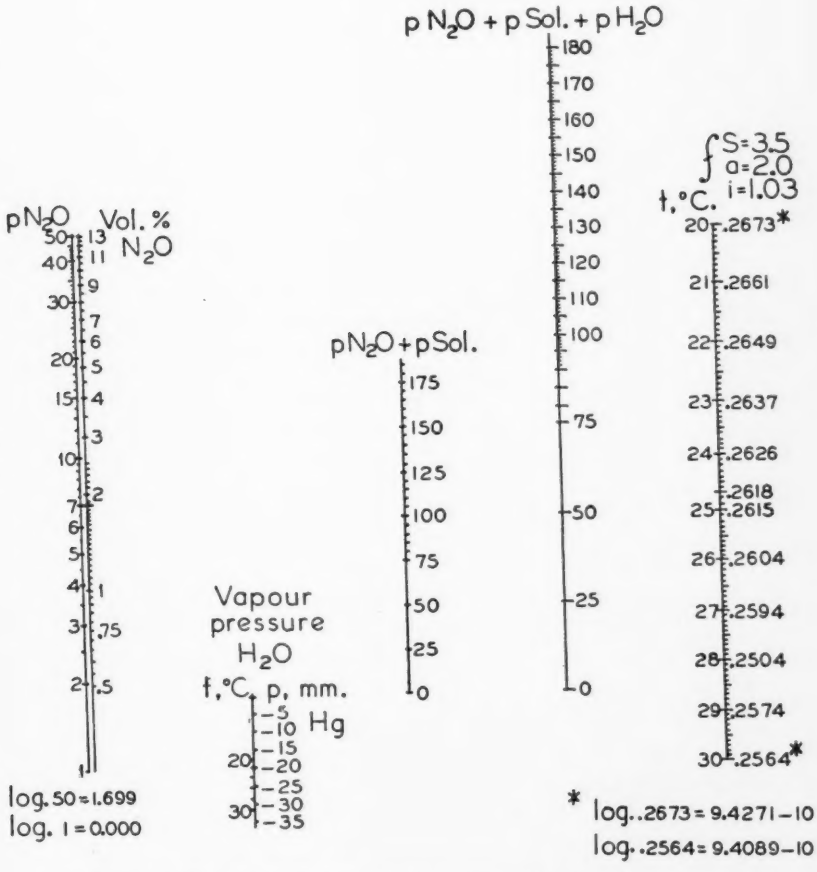

Chart 1. The nomograms presented are approximately one-half the size of the originals used. A straight edge is required to connect appropriate points. In the enlarged form calculations can be made with accuracy greater than that of the basic observations.

Technique of subsidiary observations. Rectal temperatures were recorded with a long, chemical thermometer. Stomach, skin, and room temperatures were recorded continuously with thermocouples.

A spirometer with carbon dioxide adsorbent and filled with 100% oxygen was used to measure respiratory rate, tidal air, respiratory minute volume, and total body oxygen consumption.

Possible sources of error. Possible intrinsic error in the technique has been discussed by Kety.[7, 10] It is concerned particularly with the assumptions that the specific gas employed is devoid of physiological effects in the concentration used, and that torcular blood represents a mixed sample of cerebral venous blood. In the dog, these assumptions are valid with the possible reservation that contamination of torcular blood by extracerebral venous blood may occur to a very small degree. It is of negligible significance since the form of the curves obtained indicated that equilibrium between blood and brain nitrous oxide is reached approximately as expected.

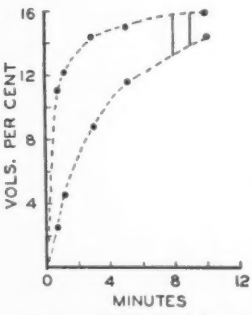

FIG. 2. The arterial and cerebral venous contents of nitrous oxide are plotted against time of inhalation of this gas. The areas of successive trapezoids one minute in width are estimated as follows: Expt. #15. The mean ordinates for ½ minute are, A = 8.0, V = 1.8; ½ minute arteriovenous difference = 6.2 which is the area of the first trapezoid from 0 to 1 minute. The mean ordinates of the trapezoid indicated from 8 to 9 minutes were $A = \frac{2.4}{2}$, $V = \frac{1.9}{2}$; 8½′ (A — V) = 2.15. The data for each minute interval are given in Table 2. See text.

Results and comment

At the time of cerebral blood flow measurement, observations were made of suitable variables to establish the experimental situation. The data, given in Table 3, are those expected for lightly pentobarbitalized dogs. The mean values obtained included: pulse rate, 162 beats per minute; mean femoral blood pressure, 133 mm. Hg; respiratory rate, 20 breaths per minute; pulmonary minute volume, 6.0 liters; arterial oxygen content, 19.2 volumes per cent; arterial carbon dioxide content, 39.5 volumes per cent; and body temperature, 38.3° C.

Cerebral blood flow. The mean of 17 measurements of CBF made in dogs was 40 ± 3.4* cc./100 gm. of brain/min. This mean is lower than either the mean of 54 cc./100 gm./min. obtained in men[10] or the 47 cc./100 gm./min. of monkeys.[14] This may be presumed to be a physiological difference. It cannot be explained by blood loss since the animals never lost more than 9% and frequently only about 5% of their blood volume, while the blood pressure never differed appreciably from its initial level at the time of the CBF measurement. Anesthesia apparently is of little significance in the range employed, compared with other variables.

Between different animals, the correlations between CBF and the factors usually implicated in changes in cerebral blood flow were calculated: arterial

* Standard error of the mean.

CO_2 content, r = .29; arterial O_2 content, r = .03; and mean femoral blood pressure, r = .31. As none of these correlations is statistically significant, the variables were probably restricted within limits too narrow to evaluate their relationships, considering the random errors involved.

Cerebral vascular resistance. The resistance to flow has been stated by Kety[10] as the pressure required to drive one cubic centimeter of blood through 100 grams of brain in one minute. The mean cerebral vascular resistance in dogs was found to be 3.6 mm. of Hg/cc./100 gm. of brain/min. This is somewhat greater than the value for men of approximately 1.7, cal-

TABLE 2

DATA FROM GRAPH, EXPERIMENT #15

t	Art. N_2O	Ven.	$(A-V)_{N_2O}$	$\int_{t-1}^{t}(A-V)dt$	$\int_{o}^{t}(A-V)dt$	$CBF = 100V_t S/\int_{o}^{t}(A-V)dt$
min.	*vol. %*					*cc./100 gm./min.*
1	...	...	..	6.20	6.20	
2	13.3	6.8	6.5	7.30	13.50	
3	14.1	8.5	5.6	6.05	19.55	
4	14.6	9.8	4.8	5.20	24.75	
5	14.8	10.8	4.1	4.45	29.20	
6	15.1	11.6	3.5	3.80	33.00	
7	15.3	12.4	2.9	3.20	36.20	
8	15.5	13.1	2.4	2.65	38.85	
9	15.6	13.7	1.9	2.15	41.00	
10	15.7	14.2	1.5	1.70	42.70	33.3 = 100· 14.3/ 42.7 V_t = 14.3

Legend:

$(A - V)_{N_2O}$ = Cerebral arteriovenous nitrous oxide difference.

$\int_{t-1}^{t}(A - V)dt$ = Area between curves A and V in Figure 2 from t — 1 to t.

$\int_{o}^{t}(A - V)dt$ = Summed areas between the same curves from o to t.

V_t = Cerebral venous nitrous oxide content at time t.

S = 1.0.

culated from data collected by Kety and Schmidt using a mean femoral blood pressure of 90 mm. Hg and a CBF of 54 cc./100 gm./min. It reflects in part the lower relative CBF in the dog, but principally the relatively high mean arterial blood pressure in this species.

Since intracerebral changes in vasomotor tone are reflected in a quantitative manner in cerebral vascular resistance, the relation between the latter and the arterial carbon dioxide content was evaluated. A non-significant correlation coefficient, r = —.37 was found, although this appears to be an improvement over the relation observed between arterial carbon dioxide content and cerebral blood flow. Conflicting influences in each animal undoubtedly prevented a more clear relation from being apparent.

TABLE 3

Expt. no.	Pulse rate	Resp. rate	Pulm. vent.	Blood pressure	CBF	CVR	CMR	A-V diff. O_2	A-V diff. CO_2	Brain R.Q.	O_2 content Art.	O_2 content Torc.	CO_2 content Art.	CO_2 content Torc.	O_2 consumed Total body	O_2 consumed Brain	Weight Total	Weight Brain	Body temp.	Sex
	per min.		L./min.	mm. Hg	*	BP/CBF	*	vol. %			vol. %				cc./min.	*	%	kg.	gm.	°C.	
75-100% Oxygen																				
4	195	10	...	130	34	3.8	1.2	3.5	3.4	.97	19.9	16.4	44.2	47.6	....	...	..	11.3	...	...	F
5a	195	20	...	135	59	2.3	1.7	2.8	4.0	1.42	17.3	14.5	48.2	52.2	....	...	..	12.1	84	...	M
5b	195	22	3.7	135	45	3.0	2.9	6.5	4.0	.62	21.0	14.5	46.5	50.5	110.8	.92	2.2	12.1	84	...	M
7a	140	16	3.3	135	31	4.4	1.2	3.8	3.5	.92	15.9	12.1	44.9	48.4	99.4	.70	1.1	14.3	91	...	M
7b	146	7	6.2	120	33	3.6	1.8	5.6	5.6	1.00	19.9	14.3	39.3	44.9	94.9	.66	1.7	14.3	91	...	M
9	202	25	5.2	140	24	5.8	1.9	7.9	7.3	.92	18.4	10.6	35.3	42.6	93.1	.78	1.7	12.0	85	...	F
10	183	30	11.2	140	66	2.1	1.1	1.7	2.8	1.65	19.3	17.6	43.5	46.3	119.7	1.11	.7	10.8	76	39.1	F
11	162	31	6.4	140	52	2.7	3.1	5.8	4.8	.83	16.4	10.6	32.1	36.9	95.2	.81	2.8	11.8	86	39.0	M
Mean	177	20	6.0	134	43	3.5	1.9	4.7	4.4	1.04	18.5	13.8	41.8	46.2	102.2	.83	1.7	12.3	85	39.1	
21% Oxygen																				
14	150	25	...	140	24	5.8	1.6	6.8	4.3	.63	21.7	14.9	36.7	41.0	198.1	.76	.8	26.0	99	39.1	M
15	144	14	...	132	33	4.0	2.7	8.2	3.4	.42	16.9	8.7	44.9	48.3	...	...	...	17.7	107	36.7	M
17	156	14	5.8	143	56	2.6	3.1	5.5	5.5	1.00	19.6	14.1	40.1	45.6	121.6	.64	2.2	19.1	85	37.2	M
18	114	19	8.3	155	32	4.8	2.8	8.9	9.0	1.01	19.6	10.7	39.5	48.5	157.9	.71	1.8	22.4	102	38.3	M
19	...	20	5.8	150	60	2.5	2.9	4.9	6.6	1.35	18.7	13.8	34.9	41.5	200.0	.96	1.3	20.9	93	38.6	F
20	130	37	6.9	105	42	2.5	3.3	7.8	7.0	.90	18.2	10.4	43.1	50.1	95.0	.75	2.8	12.7	80	38.4	M
21	166	13	5.4	120	21	5.7	2.4	11.4	10.2	.90	21.4	10.0	33.2	43.3	109.3	.64	1.8	17.1	80	36.4	F
22	...	9	3.3	110	34	3.1	3.0	8.9	8.8	.99	20.8	11.9	39.3	48.1	108.8	.79	2.6	13.8	96	36.9	M
Mean	143	19	5.9	132	38	3.9	2.7	7.8	6.9	.90	19.6	11.8	39.0	45.8	141.5	.75	1.9	18.7	93	37.7	
†12a	188	33	...	125	40	3.1	4.9	12.3	13.0	1.06	22.4	10.1	25.7	36.8	125.9	1.00	3.3	12.1	85	41.8	M
Grand mean	**162**	**20**	**6.0**	**133**	**40**	**3.7**	**2.5**	**6.6**	**6.1**	**.98**	**19.2**	**12.6**	**39.5**	**45.5**	**118.4**	**.80**	**1.9**	**15.3**	**89**	**38.3**	

* cc./100 gms./min.

† This animal breathed 75-100% oxygen.

Cerebral oxygen consumption. The relation between blood flow, A-V oxygen difference, and oxygen consumption in the brain, as described by the Fick principle, is expressed in a three coordinate logarithmic grid in Figure 3,* where the basic data of the experiments are plotted.

Eight measurements were made with animals breathing 21% oxygen. The mean cerebral oxygen consumption was 2.7 ± 0.2 cc./100 gm./min. Eight other measurements were made with animals breathing 75-100% oxygen for about 30 minutes, with a mean of 1.9 ± 0.3 cc./100 gm./min. The difference between these means was 0.9 ± 0.3 cc./100 gm./min.† This reduction is similar to the *in vitro* diminution of oxygen consumption in cerebral tissue in an atmosphere of 100% oxygen which has been reported by Elliott.[1] This may be the fundamental cerebral change in the phenomenon of oxygen poisoning which becomes most evident at two atmospheres.[6] Because of its possible clinical implications, this warrants further investigation in man, both at normal and abnormal atmospheric pressures.

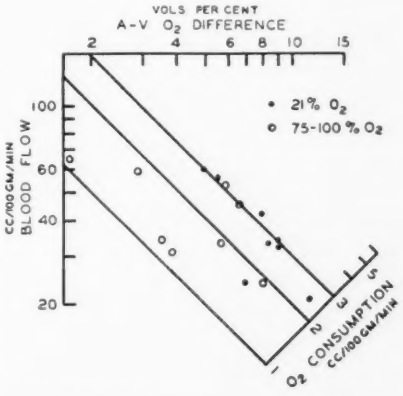

FIG. 3. Cerebral oxygen consumption is plotted as the resultant of the observation pairs of cerebral blood flow and $(A - V)_{O_2}$ difference on a logarithmic grid. The depression of cerebral oxygen uptake by high concentrations of oxygen is indicated by the comparison made between animals breathing 21% and 75-100% oxygen at the time of the cerebral blood flow measurement.

A preliminary survey in dogs indicates that a rise in body temperature is accompanied by an increase in both cerebral and the corresponding total body oxygen consumption (Fig. 4). The observations plotted were limited to those with a cerebral R.Q. within 20% of 1.00, for which a temperature measurement was available. Two of the seven observation groups were in animals breathing high concentration oxygen. The relation observed is in keeping with the known effect of temperature upon chemical reactions, and specifically the effect of temperature from 0° to 40° C. on oxygen uptake by brain tissue *in vitro* found by Field.[2]

Anesthesia is known to lower the cerebral oxygen consumption in both monkeys[14] and men.[5] Light anesthesia in dogs probably produced a slight depression below the waking state. While the exact amount is uncertain, the regular increase in both cerebral and the corresponding body oxygen con-

* Take any point, e.g., $(A - V)_{O_2} = 4$ and CBF = 80; then CMR = 3.2.
† Statistically highly significant, i.e., $P < 0.01$.

sumption noted with increased body temperature suggests that any effect is quite constant.

The mean Q_{O_2} for dogs breathing 21% O_2 was 8.1 microliters of O_2 per mgm. of dry tissue per hour, which is lower than that found for various species from studies of brain slices and homogenates, i.e., 10-15.5.[14] It is closer to the mean of 11.1 found *in vivo* in the monkey[14] and the mean of 9.9 found in man.[10] The relatively lower values found in animals and men in a near normal state, might be explained by an increase in O_2 consumption due to trauma necessarily introduced by *in vitro* study, bringing into action abnormal processes.

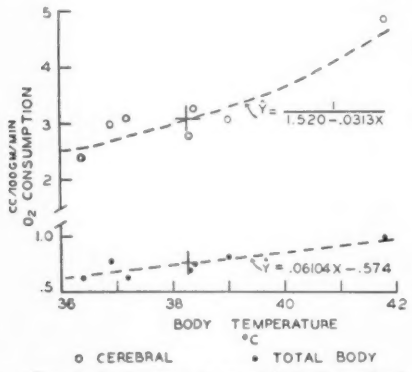

FIG. 4. An increase is noted in both cerebral and the concomitant total body oxygen consumption with increasing temperature. The calculated curves of regression give values of t = 4.36** for cerebral and t = 4.38** for total body oxygen consumption. In spite of the statistical validity of the curves, extrapolation in the range above 39° C. is not intended.

Cerebral $(A\text{-}V)_{O_2}$. Using the arteriovenous O_2 difference as a criterion, numerous attempts have been made to evaluate qualitative variations in either CBF or CMR, assuming one or the other to be constant.[16] In these experiments the $(A\text{-}V)_{O_2}$ reflects changes in both variables as is shown by the correlations: CBF, r = —.60** and CMR, r = .71.** A corollary shows that CBF alone does not determine the CMR, nor vice versa. It is apparent that it is necessary to determine both CBF and $(A\text{-}V)_{O_2}$ in order to compare individuals in different states.

Cerebral R.Q. The cerebral respiratory quotient had a mean value of 0.98. The variability was somewhat greater than is usually found, but these observations were of secondary importance to this investigation. For accurate measurements of this function, pooled blood samples are probably not ideal.

Summary and conclusions

1. The nitrous oxide method for quantitative measurement of cerebral blood flow in man developed by Kety and Schmidt has been applied to the measurement of cerebral blood flow and cerebral oxygen consumption in dogs. The details of the technique are described fully and possible sources of error are indicated.

2. Simultaneous control observations were made of suitable variables to establish the experimental conditions which were as nearly normal as possible.

3. Seventeen experiments were analyzed from a study of 22 dogs lightly anesthetized with intravenous pentobarbital. The mean cerebral blood flow was about 40 cc./100 gm./min., with a standard error of ±8.6%. The mean cerebral oxygen consumption, with dogs breathing 21% oxygen, was about 2.7 cc./100 gm./min., with a standard error of ±7%.

4. Cerebral blood flow in the dog appeared to be less than in either monkey or man, in this order, for the same quantity of brain.

5. Cerebral vascular resistance was considerably higher for dogs than for men.

6. Dogs breathing 75-100% oxygen showed no difference in cerebral blood flow from those breathing 21% oxygen, but the cerebral oxygen consumption was lower in the group breathing the higher oxygen concentration. This may be the fundamental cerebral change in oxygen poisoning.

7. Both cerebral oxygen consumption and the corresponding total body oxygen consumption were directly proportional to the body temperature.

8. Cerebral oxygen consumption in living dogs appeared to be lower than values found among various species from *in vitro* studies but was similar to the recent observations in living monkeys and men.

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PULMONARY RESECTION FOR TUBERCULOSIS*

A Report of Forty Consecutive Cases

GUSTAF E. LINDSKOG** and F. DANA LAW

No appreciation of Dr. Samuel C. Harvey's outstanding professional qualities would be complete without mention of his interest and accomplishments in the field of thoracic surgery. He was an early member of the American Association for Thoracic Surgery, and several of his former residents and assistant residents here have been stimulated to activity in that field of surgical endeavor by his example.

Like several other illustrious general surgical contemporaries, Dr. Harvey brought to the infant field of thoracic surgery a wide and sound background of basic medical knowledge and technical skills. We may recall with pride that he performed his first thoracoplasty for tuberculosis in 1926, and that this case was very likely the first in the state of Connecticut. Subsequently, his attention was directed to a study of methods for extrapleural apicolysis. He worked actively on the clinical problems of constrictive pericarditis and adhesive mediastinopericarditis. More than any other person he is responsible for the high level of surgery which has been developed in our state tuberculosis sanatoria.

It is with these thoughts in mind that we chose the following manuscript for inclusion in a *"Festschrift"* dedicated to a great surgeon and teacher.

* * *

Resection of a pulmonary tuberculous lesion is predicated to remove the principal areas of disease, thus enabling the patient to establish a more favorable immunobiologic relationship with his remaining infection and the contained tubercle bacilli. The disease process may then become totally arrested by continuing conservative measures. Resection of functionless and irreversibly damaged tissue eliminates potential sources of bronchogenic and hematogenous spread. Resection in its lobar and segmental forms is presumed also to be a relatively selective procedure. Ablation of diseased tissue may possibly save time in the future convalescence of the patient. These are the ideal considerations upon which the procedure of pulmonary resection in the treatment of pulmonary tuberculosis is based.

Resection for tuberculosis is far from being a recent and novel concept. Forlanini[5] in 1882, introducing his classical presentation on artificial pneumothorax, considered resection and thought it of theoretical value, but from the technical standpoint impractical at that time. Lojacano[6] has translated some remarks of Forlanini about pulmonary ablation: "I do not question the possibility of the operation, because the medication of Lister has let us see greater and more successful audacity in surgery. But can we think today of success in the special instance of pulmonary phthisis? . . . Experimenters limit its indication to well defined tubercular infiltrations or

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Received for publication April 16, 1951.

indurations following pneumonias limited to the apex. . . . One cannot consider the ablation of the lung in connection with the cure of phthisis except in terms of a partial resection, and the indication would be limited to extremely few cases. . . . The total or partial ablation of a consumptive lung may became a therapy of a future that one can already foresee."

These remarkable reflections, sixty-eight years before our time, were perhaps stimulating to the primitive surgical efforts of Forlanini's colleagues. Among these, Ruggi[13] in 1885 and Tuffier[14] in 1891 were the first on record to attempt deliberate resection of pulmonary tuberculous tissue; but it was not until 1935 that the possibility of resectional therapy aroused general interest. In that year Freedlander of Cleveland[6] reported a lobectomy for large cavity in a consolidated right upper lobe.

In the interim, scattered additional reports appeared regarding deliberate or inadvertent resection,[8] but the procedure gained scant adherence until 1939 when Jones and Dolley[7] reported a lobectomy, a bilobectomy, and two pneumonectomies without mortality and with apparent arrest of the disease in each case. These authors were among the first to discuss the rationale and indications for resection.

In 1942, Thornton and Adams[12] reviewed the available records in the literature. They found a mortality after pneumonectomy of 44.8 per cent and after lobectomy of 25.5 per cent, concluding that collapse measures were to be preferred to resection.

In 1943, Churchill and Klopstock[3] pointed out that 30 of the previously reported 80 cases of resection had come to operation with an erroneous diagnosis, for which reason the timing of operation and the techniques employed were not consonant with the pathology characterizing tuberculosis. They believed that the previously described results of resection were of historical interest only; they reported six new cases, in all of which the individual hilar ligation technique had been employed.

Since 1943, series of resections for pulmonary tuberculosis have appeared in increasing numbers.[1, 2, 4, 10] Advances in technique including segmental resection and the use of streptomycin have apparently lowered the operative mortality and lessened the incidence of postoperative complications. Consequently, the immediate results of resection have steadily improved. However, follow-up studies of these cases have made it evident that earlier enthusiastic reports were, to say the least, premature and that a proper evaluation of results should await a five- or ten-year follow-up period.[12]

The purpose of this paper is to review the indications for, the complications and results of, resectional therapy for tuberculosis in a consecutive series of cases treated on the Thoracic Surgical Service at the New Haven Hospital. Between April 1936 and February 1950, forty patients with pulmonary tuberculosis had pulmonary resections in some form. One patient had two lobectomies in separate operations.

Our earlier cases (prior to November 1947) did not have the benefit of

streptomycin; one patient, in fact, was operated upon in 1936 before the local introduction of sulfonamide chemotherapy. Thirty-three cases received streptomycin; seven patients did not receive the drug. Two patients had the benefit of sulfonamides alone. The regimen of streptomycin varied. Eleven of the 33 patients received the drug preoperatively, nine in a dosage of 1.0 gram per day in divided doses, two in a dosage of 1.5 grams per day, for a period of from one day to 28 days. Of the 33 patients who received the drug, all had it postoperatively. Although five of the early patients received from 1.5 grams to 2.0 grams per day in divided doses, the last 28 patients received 1.0 gram per day in divided doses. At this level the average duration of postoperative treatment with streptomycin was 19 days.

TABLE 1

RESECTION FOR PULMONARY TUBERCULOSIS (TO FEB. 1950)

Male, 20		White, 39
Female, 20		Negro, 1
Age: Oldest, 74 years Youngest, 16 years	Average 35 years	
Symptomatic duration: Briefest, 6 months Longest, 35 years Average, 8.4 years		
Endobronchial disease, 12 = 30% Contralateral disease, (preop.) 26 = 65%		
Sputum positive before operation, 29 = 72.5%		
Operative risk: Good, 14; Fair, 20; Poor, 6		

The two earliest patients in the series had tourniquet and mass ligation of the hilar structures; all subsequent cases were treated by individual ligation techniques. A four- to ten-rib thoracoplasty usually was performed following pneumonectomy if not already present. Of seven upper lobectomies, two had had a previous thoracoplasty, one had a limited apical thoracoplasty after recovery from resection, and four had no thoracoplasty in their surgical program.

Table 1 presents the vital statistics. There were 41 resections on 40 patients. Twenty-six were pneumonectomies, 17 on the left side, nine on the right. There were four bilobectomies (three R.M.L. and R.L.L.; one R.U.L. and R.M.L.) and eleven lobectomies. No segmental resections were performed in this series. The age of the patients varied from 16 to 74 years. Sixteen patients were between the age of 16 and 30, fifteen between the age of 31 and 40. Thus 31, or 75.5 per cent, were below the age of 40 years. The cases were divided equally between the sexes. There was one Negro; all others were white. The symptomatic duration of tuberculosis prior to resection varied from six months to 35 years. The incidence of known endobronchial disease, previous or present, was 30 per cent. Positive sputum just prior to resection was found in 29 cases, or 72.5 per cent. The incidence of contralateral disease prior to resection was 65 per cent (26 cases). The operative risk was estimated in three arbitrary categories. The factors taken into consideration in this rating were the age of the

patient, the general physical condition, the extent of the tuberculous lesion, and the functional ventilatory studies. From these standpoints, 14 were considered good to excellent, 20 fair, and 6 patients definitely poor operative risks.

Table 2 presents the indications for resection as they were encountered in this series. In the same table the types of operation employed and the over-all mortality are indicated. Thoracoplasty failure (13 cases), tuberculous bronchiectasis with or without bronchostenosis (12 cases), and uncontrolled cavity with or without tension (8 cases) represented the most frequent indications for resection. Less frequent indications were tuberculoma (2 cases), tumor suspects (3 cases), and fibrocaseous disease (one case). One patient represented a frank error in diagnosis. After a diagnosis of bronchiectasis, she was found to have tuberculous disease on pathological examination of the resected specimen. This case is the earliest in the series, occurred in 1936, and has been reported in the literature by one of the authors.[8]

Table 3 analyzes the complications which occurred following resection in relation to the indication for the procedure. As in other reported series,[1, 10, 12] the most frequent complications were bronchopleural fistula, empyema, pulmonary spread, and wound infections. Mediastinitis and pericarditis were rare complications. Complications most frequently occurred in those patients operated upon for uncontrolled cavity with active parenchymal disease. Of eight patients in this category seven or 87.5 were complicated—one by fistula, empyema, spread, and pericarditis; a second by fistula, empyema, and spread resulting in death; a third by spread resulting in death; a fourth by empyema and eventually fatal hemorrhage from a revised Schede thoracoplasty wound; a fifth by fistula; and two others by wound infection. It is probably significant that all eight patients in this category had positive sputum preoperatively.

Complications occurred less frequently in those patients who were considered as thoracoplasty failures. Three of 13 cases, or 23.1 per cent, were complicated—one by fistula, empyema, and mediastinitis; one by empyema; and one by a wound infection. There were no early or late deaths in the group of thoracoplasty failures.

Fistula, empyema, spread, mediastinitis, wound infection, and eventual death in the 19th postoperative month occurred in the patient with mistaken diagnosis. This series of events well illustrates the disastrous consequences of such an error and the use of the now outdated mass ligation technique. A minor wound infection occurred in one of the three patients who were tumor suspects.

There were no complications in those patients operated upon for tuberculous bronchiectasis or bronchostenosis, tuberculoma, or chronic fibrocaseous disease without cavity.

In summary, 12, or 30 per cent, of the 40 cases had postoperative compli-

TABLE 2. INDICATIONS FOR RESECTIONAL THERAPY

	Type of operation				Deaths		
	Total Cases	Lobectomy	Bilobectomy	Pneumonectomy	T.B.	non T.B.	Time postop.
I. Thoracoplasty failure	13	1	1	11	0	0	...
II. Bronchostenosis, bronchiectasis	12	2	2	8	0	1	6 yrs.
III. Uncontrolled cavity (2 tension)	8	2	1	5	3	0	19 mos. 2 " 8 "
IV. Tuberculoma	2	2	0	0	0	0	...
V. Tumor suspects	3	2	0	1	0	0	...
VI. Fibrocaseous disease	1	1	0	0	0	0	...
VII. Mistake in diagnosis	1	0	0	1	1	0	19 mos.
Total	40	10	4	26	4	1	

TABLE 3. COMPLICATIONS OF RESECTION FOR TUBERCULOSIS

Group	Total cases	Cases complicated	Per cent	Type of complication						
				Fistula	Empyema	Spread	Mediastinitis	Pericarditis	Wound infection	Death
I. Thoracoplasty failure	13	3	23.1	1	2	0	1	0	1	0
II. Bronchiectasis-stenosis	12	0	0.0	0	0	0	0	0	0	0
III. Uncontrolled cavity (2 tension)	8	7	87.5	3	3	3	0	1	2	3
IV. Tuberculoma	2	0	0.0	0	0	0	0	0	0	0
V. Tumor suspects	3	1	33.3	0	0	0	0	0	1	0
VI. Fibrocaseous disease	1	0	0.0	0	0	0	0	0	0	0
VII. Mistake in diagnosis	1	1	100.0	1	1	1	1	0	1	1
Total	40	12	30.0	5	6	4	2	1	5*	4
Per cent		30%		12.5	15.0	10.0	5.0	2.5	12.5	10.0

* 4 healed

cations of some type and of major or minor degree. The over-all incidence of postoperative bronchopleural fistula was 12.5 per cent, empyema, 15 per cent, and spread (unilateral or contralateral), 10 per cent.

Table 4 correlates the preoperative sputum record with the complications of resection and mortality. Of the eleven patients who had a negative sputum preoperatively, two, or 18.2 per cent, had postoperative complications. One had a minor wound infection; the second had fistula, empyema, and spread, and died (9.1 per cent). The latter was the patient with the mistaken diagnosis, and it is very likely that tubercle bacilli were in her sputum although not found preoperatively after repeated searching. Of the 29 patients with positive sputum preoperatively, 10, or 34.5 per cent,

TABLE 4

CORRELATION OF PREOPERATIVE SPUTUM WITH RESULTS OF RESECTION

	Cases	*Complications*	*%*	*Deaths*	*%*
Sputum negative	11	2	18.2	1	9.1
Sputum positive	29	10	34.5	3	10.4
Total	40	12	30.0	4	10.0

had complications of resection. There were three late deaths in this group, or 10.4 per cent.

Pathological examination of all 41 resected specimens revealed pulmonary tuberculosis.

Table 5 shows the results of resection and the present status of the patients in this series through June 1950. The majority of the patients have been followed up to three years, the earlier cases longer. Although there was no postoperative hospital mortality, five patients are now dead, four of them having died as the result of tuberculous complications; one patient died of rheumatic heart disease. Of the 35 survivors, 31 are carrying on light or moderate activity in the business world, are studying at school, or are maintaining a home. All 31 of these patients have either no sputum or negative sputum, and their disease is apparently arrested by serial roentgen study. Four patients are still "curing" in sanatoria. They are reported to have negative sputum, and by X-ray examination they have arrested their disease. Two of these patients, however, have Schede thoracoplasty wounds, incident to the treatment of empyema, which are slowly closing; a third has recently finished a course of chemotherapy to heal a laryngeal lesion; and a fourth is convalescing well from his recent operation.

In conclusion, we feel that pulmonary resection has earned a definite place in the therapy of pulmonary tuberculosis. The use of the individual

hilar ligation technique, the increasing benefits of the antibiotics, and more recently segmental resection are widening the scope of excisional therapy. Acceptable indications include thoracoplasty failure, bronchiectasis with or without bronchostenosis, chronic empyema with destroyed lung, tuberculoma, and tumor suspects. Because of the unfortunate results of resection in that group of eight patients characterized by uncontrolled cavities, active parenchymal infiltration, and highly positive sputum, it is felt that primary resection is not at present the ideal treatment for such patients. But it is evident that a final and truer evaluation of the efficacy of pulmonary resection for tuberculosis must await further development of the method and a follow-up period of not less than ten years.

TABLE 5

PRESENT STATUS OF CASES, JUNE 1950

	Living			*Dead*
Duration of follow-up	*School or working*	*Curing*	*Total*	
5 plus years	1	0	1	1
4-5 years	1	1	2	0
3-4 years	1	0	1	0
2-3 years	12	0	12	1
1-2 years	11	2	13	2
6 months	4	1	5	0
Less than 6 months	1	0	1	1
Total	31	4	35	5

Summary

1. A series of 40 consecutive cases submitted to pulmonary resection for tuberculosis has been presented.

2. The indications for excision, the complications, and the results of the procedure have been discussed.

ACKNOWLEDGMENT

The authors wish to thank staff members of the Laurel Heights, Undercliff, Cedarcrest, and Uncas-on-Thames State Tuberculosis Sanatoria, the Gaylord Farm Sanatorium, and those private physicians who are following several of the patients in the series for their co-operation in the preparation of patients for surgery and in the follow-up studies.

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THE EFFECT OF TRAUMA ON WOUND HEALING
An Experimental Study*

MAX TAFFEL,** ARTHUR J. DONOVAN, and LUCIAN S. LAPINSKI

The exact nature of the stimulus that initiates and sustains wound healing is not known. It seems probable that when tissues are injured, some type of growth-promoting substance is elaborated.[9] These substances have been referred to by a wide variety of terms,[1, 2, 7] the most common of which is "wound hormones."[4] Some have felt that these hormones remain only in the immediate vicinity of the traumatized tissues and are capable therefore of exerting only a local and circumscribed effect. Others have conceded the possibility that the hormones may be absorbed and carried by the circulating blood to all parts of the body. If the latter hypothesis were correct, it would be reasonable to expect that a wound made at a time when the titer of these hormones in the blood was high would heal at a more rapid rate than under normal conditions.

In 1941, Young, Fisher, and Young[10] studied the effect of the presence of one superficial skin wound upon the rate of healing of a second similar wound made after an interval of ten or twelve days. Rabbits weighing from 2.0 to 2.5 kilograms were used exclusively. The rate of healing was measured by a planimetric method. All the wounds were left open and undressed. On the basis of a relatively large number of experiments, the authors arrived at the conclusion that in seven out of their ten series the secondary wounds healed at a significantly more rapid rate than the primary wounds. This work, although thoughtfully conceived and carefully executed, is subject to a number of serious criticisms, some of which the authors themselves recognized and acknowledged. Firstly, the use of open wounds introduces such gross factors as: (i) direct mechanical trauma to the wounds, (ii) chemical contamination by food, urine, and feces and, (iii) unlimited bacterial contamination. These factors are variables that can be neither controlled nor accurately measured. Secondly, the wounds were not all treated exactly alike. In order to minimize bleeding immediately after the operation, adrenalin pledgets were applied to some of the wounds and acriflavine to others. Thirdly, because the wound margins slid freely over the underlying tissues and because the size and shape of the wounds varied considerably with the stance of the animals, the method of measuring the wound was not easy or exact. Fourthly, the fact that the end-point of

* From the Department of Surgery, Yale University School of Medicine. Aided by a grant from the Reckford Research Fund, Yale University School of Medicine. Presented at the meeting of the Society of Clinical Surgery on November 10, 1950 in New Haven, Connecticut.

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Received for publication April 25, 1951.

healing was not always sharp and precise may have been another source of error. Finally, the authors did not have a true "control" series in their experiments. The secondary wounds were made at a time when the primary wounds were still open and actively healing. Both sets of wounds, present and healing in the same animal at the same time, were therefore in a position to influence each other, and it would not be fair or reasonable to assume, without further evidence, that that influence was exerted only in the direction of the primary wounds upon the secondary wounds but not vice versa.

In 1949, Sandblom,[8] working on the same problem in rabbits, reported similar results. He made two skin incisions, one in front of the other, on the back of each animal. After five days the wounds were excised and their tensile strength was determined by a tensiometer. Fifteen days after the first wound had been inflicted, two new similar incisions were made on the other side of the back. These, too, were excised on the fifth day of healing and their tensile strength measured in the same way. Using this basic pattern, the author, in subsequent experiments, varied the interval between the primary and secondary wounds and the days on which tensile strength determinations were made. He concluded that the secondary wounds healed more rapidly than the primary wounds and, among other things, that the healing curve of the former wounds exceeded that of the latter throughout the first ten days of healing. These experiments are subject to some of the same criticisms as those of Young, Fisher, and Young. The wounds were all on the surface and were therefore exposed to variable influences. Furthermore, as Sandblom pointed out in his report: "A major drawback to the method . . . is that the primary or control wound is identical with and hence inseparable from the stimulus, i.e., the injury. When therefore the control is altered—for example, for studying the strength of wounds at different stages in order to construct the healing curve—the stimulus is changed accordingly. Moreover, the injury is two-fold—it consists of inflicting the wound and excising it later for examination. These facts must be borne in mind when the results are evaluated."

When the present experiments were planned, an attempt was made to profit by the work of previous investigators and to avoid as far as possible some of the difficulties which they had encountered. The primary wounds, involving skin, subcutaneous tissue, fascia, and muscle served only as the source of trauma. They were not also used as controls. The experimental and control wounds were made in the stomachs of separate animals, and every effort was exerted to keep all the conditions identical. Furthermore, the fact that the healing of stomach wounds has been studied intensively under a wide variety of circumstances provided a good base-line for evaluation of the results to be obtained here, not only in the experimental wounds but in the control wounds as well. Young, growing white rats, all of the same strain and each weighing about 100 grams, were used. The

animals were kept in cages under ordinary laboratory conditions and were offered water and a complete diet *ad libitum*. They thrived on this regime and continued to gain weight at a normal rate.

Series A. Experimental group—50 animals. A measured 4 cm. incision was made in the interscapular area, to one side of the midline, and extended through the skin, subcutaneous tissues, and paraspinous muscles down to the bony thoracic cage. The wound was then carefully closed in two layers with fine silk sutures. Five days later the secondary wound was made. This consisted of an incision measuring 1 cm. in length and extending completely through the wall of the cardiac portion of the stomach. The wound edges were immediately approximated in one layer with a running, continuous Connell suture of #000 plain catgut, which loses its tensile strength well within four days.[6] The abdominal wall was closed in two layers with fine silk sutures. The operative procedures were performed under drop-ether anesthesia, and strict aseptic technique was observed. On each of the 4th, 6th, 8th, 10th, and 12th postoperative days ten animals were sacrificed. The strength of the stomach wounds of eight of these was immediately determined by distending the stomachs with air and measuring the bursting pressures;[5] the stomachs of the remaining two animals were preserved intact for histological examination.

Series A. Control group—50 animals. The above regime was carefully duplicated in every particular, including the two administrations of ether anesthesia but omitting the infliction of the primary wound. Histological studies and determinations of the tensile strength of the stomach wounds were similarly made from the 4th to the 12th postoperative days.

Series B. Experimental and control groups—100 animals. This series differed from Series A only in the respect that the stomach wounds were made fifteen days after the primary wounds instead of five days.

With rare exceptions, the primary and secondary wounds in Series A and B healed *per primam*. The few animals that demonstrated evidence of wound infection, even if only of minor degree, were discarded. The averages of the bursting strengths for each postoperative interval and the standard deviation were computed. Fisher's[3] formula for small samples was applied to determine statistical significance.

Results

The curves of healing of the secondary stomach wounds in both series showed no statistically significant deviation from normal (Charts I and II). Histological examination also failed to show any constant or appreciable variation in the degree of exudative or fibroblastic response. The tensile strength of the wounds could be measured accurately only during the 4th, 6th, and 8th postoperative days, when the stomachs burst almost invariably through the wounds. On the 10th and 12th days, in both the experimental and control animals, the bursting points were located more often in some part of the intact stomach wall than in the wounds themselves. The absolute strength of the wounds in these latter two periods of healing could therefore not be determined by this method, and all that can be said is that the wounds in both the experimental and control groups were stronger than the adjacent stomach walls.

Conclusions

In young, growing white rats, trauma in the form of relatively large, soft tissue wounds did not affect the rate of healing of secondary wounds in the stomach that were made after five and fifteen days respectively. These experiments lend further confirmation to the concept, already firmly supported by other data, that a healing wound is a basic and elemental biological process that proceeds autonomously at its own constant pace, un-

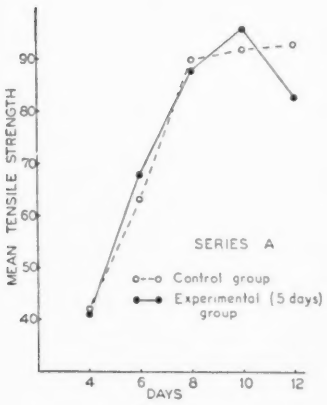

CHART I

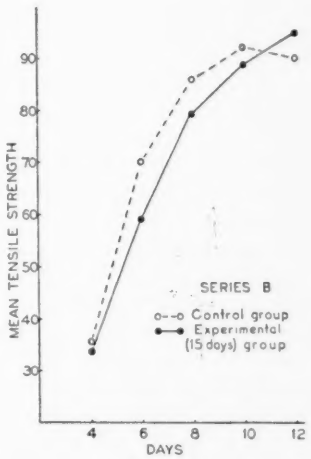

CHART II

altered and undisturbed by any but the most overt and gross stimuli. Wound sepsis, severe hypoproteinemia, and almost total vitamin C deficiency may impair or retard wound healing, but an influence that clearly and indisputably accelerates it still remains to be demonstrated.

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SUGGESTIONS CONCERNING THE USE OF THE SUBCLAVIAN WHICH ARISES FROM THE AORTA IN THE TREATMENT OF THE TETRALOGY OF FALLOT*

HARRIS B. SHUMACKER, JR.**

In Blalock's early experience with the operative treatment of the tetralogy of Fallot, the two subclavian, the innominate, and carotid arteries were all used for anastomosis to the pulmonary artery. Soon, however, it became evident that use of the innominate or carotid was followed by a relatively high incidence of complications resulting from cerebral ischemia. Blalock suggested, therefore, that the subclavian be used by preference. The subclavian branch of the innominate does not become kinked or badly angulated when it is turned down for the anastomosis, and a good functional result almost invariably follows the completion of a satisfactory anastomosis. The subclavian which arises directly from the aorta, on the other hand, tends to form a bad angle when it is brought down for the anastomosis, and, indeed, near its point of origin it may be so flattened out against the relatively rigid aortic wall as to obstruct all blood flow through it. These considerations led Blalock to recommend the use of the former except in infants under two years of age in whom this artery may be too small and in adults or children over twelve years old or five feet tall with a left aortic arch in whom it is often too short to permit a satisfactory anastomosis.[1, 2]

In contrast, Paine and Varco,[6] Lam,[8] Holman,[4] Olim,[7] and others have preferred to use the subclavian which arises from the aorta and have obtained generally excellent results. They point out that the tendency to kinking of the artery is more a theoretical than a practical disadvantage, that the exposure and dissection of both the pulmonary artery and the subclavian are easier on the side of the aortic arch, that both vessels are generally longer than on the opposite side and that, as a general rule, the anastomosis can be accomplished more readily. The practical usefulness of a third systemic vessel, namely the aorta, was demonstrated by the development of a technique for side-to-side aortic pulmonary anastomosis by Potts and his associates.[10] In spite of the preferences held by individual operators for use of one vessel or another, the fact remains, as Blalock has emphasized, that there is always present a usable systemic vessel provided a suitable pulmonary artery is available. Nevertheless, the choice of the systemic artery in each individual patient is important since in certain cases one or another is unsuitable.

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Received for publication April 26, 1951.

It has been my custom to follow a policy rather similar to that outlined by Blalock. The subclavian branch of the innominate has generally been preferred in patients ranging between two and twelve years of age and in older individuals in whom there is a right aortic arch. In others the thoracotomy is usually made on the side of the aortic arch, and either the aorta itself or the subclavian arising from the aorta is used for the anastomosis. My experience with the use of the subclavian originating from the aorta is small and the results have not been as good as those which others have reported. One eighteen-month-old child died the day after operation and was found at post-mortem examination to have an occluded anastomosis. In one three-year-old child and one twenty-year-old woman a poor result was obtained and a second operation upon the other side was necessary. In two additional cases the result was only fair. Excluding the patients mentioned in the present report, only in two was an unquestionably good result obtained.

Recently, in several cases in which failure seemed evident a modification has been required in order to obtain a functioning shunt. Since these modifications proved successful and since these threats of failure tax one's ingenuity at the time of operation, I have thought it might be helpful to describe the procedures employed and to illustrate them with case reports. One is a method which obviously has very limited applicability, while the other would seem to be rather generally applicable.

The first consists of the transplantation of the origin of the subclavian to a more suitable portion of the aorta.

Case report

The patient was a 19-year-old girl who had been cyanotic since the age of six months. She had developed normally but was always limited in exercise capacity. In her early years of school she was taken to school by her parents and carried to and from her seat in the classroom. She did reasonably well in high school, being driven to and from the school, but she got into severe difficulty when she attempted to attend college. The longer distances between classes and the necessity for climbing stairs precipitated a downhill course, with increasing dyspnea, more marked cyanosis and fatigue, and the onset of bouts of loss of consciousness. The latter occurred several times daily. One which was witnessed by her physician lasted 45 minutes; he feared it would prove fatal. Ordinarily, she could not walk more than half a block.

There was marked cyanosis of the nails and mucous membranes and to a lesser extent of the skin. Clubbing was very prominent. All the results of physical and laboratory examination fitted in with a diagnosis of tetralogy of Fallot. The hematocrit ranged between 83 and 90. Oxygen saturation of arterial blood was 65 per cent at complete rest. The aortic arch was on the left side. On October 26, 1949 a left lateral thoracotomy was performed, the pleural cavity being entered through the bed of the fifth rib. There was evident greatly increased collateral circulation in the mediastinum and hilum. The pulmonary artery appeared to have markedly reduced blood flow, was very short, small, and thin-walled. Its diameter was less than 5 mm. The aorta seemed to be bowed out laterally in an unusual fashion and the short pulmonary artery could not possibly be brought out over it. The subclavian artery was relatively small, having

a diameter of only about 4 mm. but it seemed rather long. It was apparent that a Pott's procedure was impossible and that an end-to-side subclavian pulmonary artery anastomosis would be doomed to failure. Hence, the subclavian artery was divided at the level of its first branch, the pulmonary artery was divided proximally, and an end-to-end subclavian-pulmonary anastomosis was carried out. This was done with ease. When the clamps were removed, however, no blood flowed through it. The soft-walled subclavian was completely flattened out against the relatively rigid aorta (Fig. 1). When the hilar structures were forcibly elevated in a cephalad direction the subclavian immediately filled and pulsated normally and a thrill could be felt. Simple expansion of the lungs, however, failed to achieve this result and I could conceive of no way in which the hilar region could be held in a more cephalad direction. The subclavian was then ligated at the point where it came off the aorta and its proximal end was anastomosed end-to-side to the descending aorta. It now pulsated vigorously as did the pulmonary artery. In spite of the good pulsation no thrill was palpable. The patient had an uneventful but disappointing convalescence. She remained markedly cyanotic and no continuous bruit was audible. When she left the hospital 14 days after operation there was no improvement in her appearance, hematocrit, or arterial oxygen saturation.

Surprisingly enough she reported progress on each follow-up examination. By the end of seven weeks she was obviously less cyanotic, her hematocrit was 77, and she was able to walk a number of blocks and to climb a flight of stairs without difficulty. She reported that she had danced and roller-skated without much trouble. Shortly thereafter a continuous murmur was audible in the left chest. She continued to improve and in January entered a southern college. She did well. At least once a day, often twice, she walked without difficulty from the campus into town and back, a distance of ten blocks each way. She played a little tennis, learned to swim, and began to dance, including jitterbugging. When she was seen in June, her color was good, although there was still slight cyanosis of lips and nail beds. There was a very loud, continuous murmur in the left chest. The following fall she transferred to a midwestern university. She got along reasonably well but not as well as she had in a warmer climate and on more level terrain. She walked four or five blocks up and down hills between classes without difficulty in good weather but complained of some dyspnea and fatigue on cold, windy days. She attended dances and often danced each number throughout the evening without trouble. When seen in December she looked well. Her color was good and clubbing was definitely less marked than it had been previously. She had a severe cold at the time. Her oxygen saturation of arterial blood was 75 per cent at rest and it did not fall when she stood or still-walked. The hematocrit was 69. There was audible the same loud continuous murmur in the left chest.

Though the patient has been markedly improved, it is recognized that the result is not as good as is commonly obtained when patients with more adequate pulmonary arteries are treated by the conventional anastomosis of a systemic artery to the side of the pulmonary artery. Nevertheless, the patient has thus far been given such good health and relatively normal capacity for ordinary activity that further operation has seemed unwarranted, though the possibility of some future attempt at creation of an additional shunt is being kept in mind.

The second procedure embodies the cephalad transplantation of the pulmonary artery by a plastic repair of the incision in the hilar and mediastinal pleural structures.

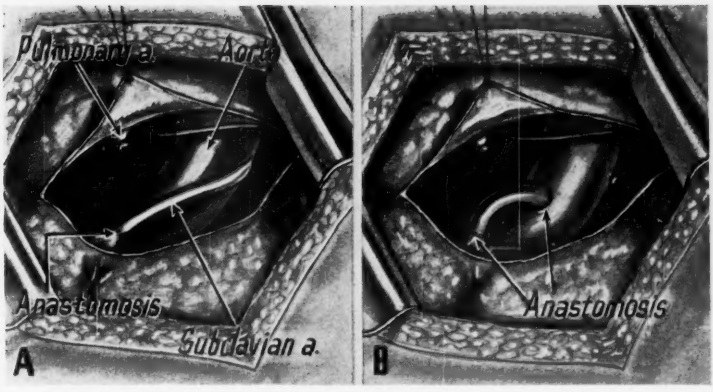

FIG. 1. Drawing illustrating the condition which existed in the first case after completion of the anastomosis (A) and its correction by transplantation of the origin of the subclavian (B).

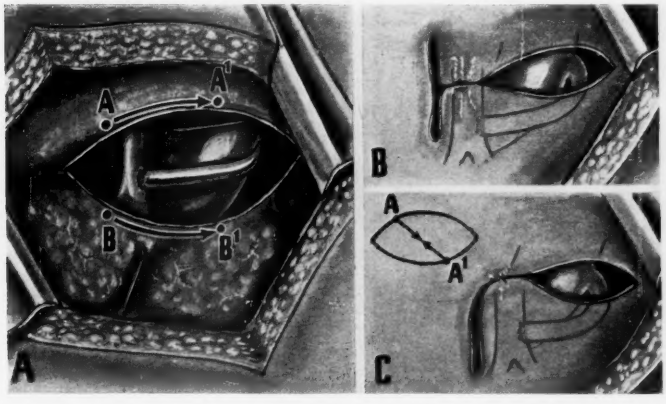

FIG. 2. Drawing illustrating correction of obstruction to blood flow through the subclavian artery by inverted T or L plastic closure of the defect in the hilar and mediastinal structures.

Case reports

The first patient was a fully grown young man of 17 with tetralogy of Fallot which caused considerable incapacity. He was admitted to the hospital on July 18, 1950 and was operated upon two days later. He was known to have a left aortic arch, and a left lateral thoracotomy was performed. The aorta was freed for a side-to-side anastomosis with the pulmonary artery. So much difficulty was encountered, however, in placing the aortic clamp in proper position for making a satisfactory incision in the aorta that the procedure was abandoned and an end-to-side subclavian-pulmonary artery anastomosis accomplished instead. The pulmonary artery was of fair size, having an estimated diameter of 1 cm. The subclavian artery appeared to be quite long and it was of very satisfactory size, having a diameter of about 6 mm. To my dismay, the first portion of the soft-walled subclavian artery was completely flattened out against the rather rigid wall of the aorta and no blood flow through it could be demonstrated, there being no subclavian pulsation nor thrill in the pulmonary artery. If one forcefully elevated the hilum of the lung in a cephalad direction, the obstruction disappeared, the subclavian artery began to pulsate, and a thrill could be palpated. When the lung was allowed to assume its usual position, the subclavian obstruction was again evident and could not be prevented by full expansion of the lung. It was found that the hilar region and the pulmonary artery could be maintained in a satisfactory cephalad position by traction upward upon the cuff of hilar pleura and the adjacent vascular sheath and that these structures were sufficiently strong so that traction could be maintained upon them with a small hemostat. The defect in the mediastinal and hilar tissues was then repaired using a sort of inverted T-plastic closure. By this maneuver success was achieved in elevating the pulmonary artery in a cephalad direction so that the subclavian obstruction was relieved and excellent pulsation was evident (Fig. 2B). A fairly good continuous thrill was palpable. The patient had an uneventful convalescence. When last seen on January 16, 1951 he had excellent color without any visible cyanosis. The clubbing seemed to have decreased somewhat. A continuous murmur was audible. He stated that he noted no limitation of exercise capacity. In outlining his activities he said that, among other things, he was doing a great deal of ice-skating and was playing ice hockey regularly. He was planning to start college work the following month.

The second patient was a 16-year-old boy who had been cyanotic since birth. His physical development was somewhat retarded and he was slow in learning to sit and walk. Until he had grown old enough to be self-conscious about it he had always squatted when he was tired. By perseverance he had managed to do more than one would have suspected he could from the degree of his cyanosis. He could walk as much as five or six blocks at a slow pace. He was fond of drums and managed to play occasionally with an orchestra in a somewhat restricted fashion. For the past few months he had had more dyspnea, fatigability, and seemed to be going downhill generally.

The results of physical and laboratory studies were rather typical of the tetralogy of Fallot. Clubbing was marked, the nailbeds and mucous membranes were a rather deep purplish-blue color, and the skin had a dusky cyanotic tint. The aortic arch was determined to be on the left. On July 21, 1950 a left lateral thoracotomy was performed, the pleural cavity being entered through the bed of the fourth rib. There was a rather marked increase in the collateral circulation in the mediastinum and the hilar region. The pulmonary artery was easily dissected free. It was fairly long and was about 1 cm. in diameter. The subclavian artery seemed quite long and was of adequate size, having a diameter of about 5 mm. An end-to-side subclavian pulmonary anastomosis was performed. Again in this case, however, the first part of the subclavian was acutely angulated and completely flattened out against the aortic wall. There was no

pulsation in the subclavian and no thrill in the pulmonary. In this instance also, good blood flow through the subclavian artery was evident whenever the hilar structures were elevated in a cephalad direction but no pulsation was demonstrable simply by expanding fully the lung. Again, a sort of inverted T-plastic closure of the defect in the hilum and mediastinum brought about a cephalad elevation of the pulmonary artery so that tension was released and there was excellent pulsation in the subclavian artery. A thrill was now palpable. Convalescence was uneventful. Improvement in color was evident within a few days and his color was excellent by the time he was discharged from the hospital on the thirteenth postoperative day. He rapidly found that he was now able to lead a quite normal sort of life. When he was seen on December 9 he stated that he had no limitation in exercise capacity. He could walk rapidly without fatigue. He was going to school and was playing the drums in a professional orchestra three or four nights each week. There was some diminution in the clubbing and his color was excellent. There was a loud continuous bruit audible in the chest. On March 27 the arterial oxygen saturation was 88.2 per cent.

When I first used this procedure I was rather surprised that such tissues would hold sutures and serve satisfactorily to elevate the hilum. On occasions I had previously toyed with the idea of suturing hilar pleura to the mediastinal pleura but had abandoned it as impractical because the sutures seemed to pull out whenever there was any tension whatsoever. If the procedure is to be successful, it is essential that the sutures encompass any adjacent areolar and fibrous tissue and especially the so-called vascular sheath which surrounds both pulmonary artery and aorta and is dissected free during the course of the operation. Fortunately, in its proximal portion the sheath about the pulmonary artery gains added strength from the extension into it of a reflection of the fibrous pericardium. Sutures through the mediastinal pleura in the region of the aortic arch purposely include the perivascular tissues which have been stripped off the aorta and subclavian artery and also any other available tissue which may lend strength, such as the divided ends of the supreme intercostal vein or other vessels which have been transected and ligated. The exact method of repair will vary from case to case. By placing the sutures properly it would seem possible sometimes to displace the pulmonary artery laterally as well as in a cephalad direction if such a maneuver was thought to be desirable (Fig. 2C). On occasions one would close the pleural defect fairly snugly, on others leave it wide open in places.

Discussion

Though there is always available some suitable systemic vessel and though the major concern in the operative treatment of the tetralogy of Fallot is the adequacy of the pulmonary artery, from time to time one may find the achievement of a satisfactory result thwarted by the local anatomical characteristics regardless of one's choice of procedure. Consequently, those modifications which may add to the likelihood of a successful outcome are important. Blalock[1,2] pointed out the practicability of performing an end-to-end subclavian-pulmonary artery anastomosis whenever the pulmonary artery is judged too small or the subclavian too short for a satisfactory end-

to-side anastomosis. Holman[4] feels that a poorly functioning shunt after end-to-side anastomosis can usually be corrected by proximal division of the subclavian artery, thus in effect converting the procedure into an end-to-end anastomosis. If a satisfactory end-to-side suture of subclavian and pulmonary arteries or side-to-side aortic pulmonary anastomosis seems difficult to achieve, one may occasionally find it useful to divide the upper lobe branch of the pulmonary artery and carry out an end-to-end suture of the subclavian and the proximal end of the upper lobe branch. Potts and Smith[6] performed an anastomosis between the proximal end of the upper lobe branch and the side of the aorta in a case in which complete temporary occlusion of the main pulmonary artery was withstood poorly. I have found this principle of division of the upper lobe branch and use of its proximal end of value in obtaining a suitable subclavian pulmonary anastomosis when the subclavian seemed to have inadequate length. On occasions when the systemic vessel seems too short, one may elect to interpose a free vascular transplant,[3, 5] a modification I first employed in 1946 though unfortunately not with success in this instance.

The operation performed in my first patient constitutes in reality the use of the subclavian artery as an autogenous graft between the aorta and pulmonary artery. It will obviously not often be the procedure of choice but sometimes may be found a useful measure in converting an apparently inadequate functional shunt into a good one. If my initial experiences with the plastic repair of the defect in the mediastinal and hilar structures are characteristic of what may be expected of this procedure, it would seem to have wide applicability whenever a poorly functioning subclavian-pulmonary shunt seems correctable by cephalad transplantation of the hilar structures and the consequent release of tension. I was unaware of any reference in the literature to its use until belatedly I discovered that I had overlooked a statement in the legend of one of the excellent drawings in Blalock's paper on surgical procedures in pulmonic stenosis.[2] Here he states that suture of the pleura of the superior aspect of the hilum to the mediastinal pleura may effectively elevate a little the pulmonary artery. Perhaps our more detailed consideration of this maneuver may add to its general usefulness.

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FRONTAL LOBE SURGERY IN TREATMENT OF INTRACTABLE PAIN*

A Critique

JAMES PETER MURPHY**

Improvement in methods of dealing with complications of debilitating illnesses has resulted in prolongation of the lives of many patients suffering from chronic, painful conditions—notably, cancer—far beyond that of previous expectancy. The number of individuals afflicted by unbearable pain is on the increase, and dissemination of information concerning extension of pain-relieving technique has resulted in so many demands for relief, to the medical public, as almost to create a sub-specialty, the "pain clinic."[3]

Semmes[30] has listed fundamental principles to be considered in the treatment of the pain patient. These are: (i) Location of the pain; (ii) accessibility of pathways; (iii) desired duration of interruption (of pathways); (iv) physical, mental, and economic status of the patient; and (v) in general, the simplest effective measure.

One of life's truisms is to the effect that one never receives "something for nothing." Grant[8] has well said that "the methods at one's disposal for the relief of pain are not completely satisfactory," by which is meant that deficit signs and symptoms are invariably after any surgical procedure directed towards interruption of pain-pathways at whatever level. The search for the "ideal" procedure—isolation of the individual from pain by operation at the highest level—seemed to have ended with the introduction of prefrontal lobotomy into the pain problem, in 1943.[8] Since then, a great many reports concerning various types of operations upon the frontal lobes of the brain, designed to relieve sufferers from intractable distress, have appeared in the medical literature of the world. Experience accumulated during a period of eight years may now allow some observations in regards to the *pro* and *con* of lobotomy for pain, deficit symptoms, selection of cases, and the like.

Theoretical considerations

Exactly how frontal incision eliminates complaints of unbearable agony, when it does, remains a mystery. Jeremiah Kurtz, the deified protagonist of Joseph Conrad's *Heart of Darkness,* said "Pain and pleasure are emotions, not sensations," and modern neurophysiology has done little to alter

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Received for publication April 10, 1951.

this view. The balance of opinion holds that lobotomy relieves by the production of traumatic euphoria, asymbolia for pain, or an organic confusional syndrome. Watts and Freeman[24] believe that "psychosurgery changes the individual's reaction to pain without materially changing his ability to feel pain. Pain may be present, but when divorced from its implications . . . becomes bearable and may be accepted with fortitude." Koskoff[11] has designated the effect of operation as abolition of "suffering" rather than "pain." Krayenbühl[12] notes that absence of complaints after operation persists just so long as psychic disturbance remains present—an observation that is not necessarily correct, but represents an orientation.

An explanation of relief as a feature of a surgically-induced psychosis is probably over-simplification. It does not apply to the individual whose pain (from cancer) is not associated with symptoms of anxiety or fear, and who is relieved by lobotomy for longer periods of time (see below). It is common observation that boring, deep, all-pervading pain (from pelvic carcinoma, for example) is in abeyance after operation, whereas lancinating attacks resultant from intestinal cramps or motion of a partially paralyzed leg persist. Experimental findings of decrease rather than increase of "bright pain" threshold after frontal surgery are mentioned to emphasize this discrepancy.[3]

Experimental theory suggests that pain impulses may synapse in hypothalamic-thalamic nuclear masses and project from there to the frontal and temporal cortex which curves around the lesser wings of the sphenoid bones. If present, such pathways to consciousness are interrupted by the performance of prefrontal lobotomy. Evidence has been presented by Spiegel and Wycis[22] that coagulation of the dorsomedial thalamus may produce the same effect. Retrograde degeneration of the medial thalamus is known to follow frontal section.[7]

Varieties of operation

Attempts are being made constantly to modify prefrontal lobotomy to suit the pain patient, with an ideal goal of maximal benefit and minimal deficit. It is the opinion of the author, before discussion of various modifications of the original lobotomy method, that nothing has been developed which is definitely superior.

Autopsy studies[14] reveal great discrepancy between anticipated plane of subcortical section and actual cut, whether the method is "open" or "closed," and there is also enough lack of correlation between degree of pathway-interruption and postoperative change in the patient to give food for thought. It is stated of each variation that beneficial effects remain but that undesirable side-reactions are minimized. "Minimal" lobotomy (lower quadrants of each frontal lobe) was first proposed by Watts and Freeman. Next followed unilateral lobotomy, introduced by Scarff[19] and Rowe.[18] Grantham[10] advised bilateral sectioning of medial frontal fibers from above. Transorbital

lobotomy[5, 6] is also being used. The most significant changes in surgical approach are those of Spiegel and Wycis[22] (thalamotomy) and of Pool[16] and LeBeau.[12] The latter authors advocate removal of blocks of frontal cortex (areas 9, 10, 46—Brodmann) and state that pain relief is good after such operation ("topectomy") and that disagreeable psychic concomitants are few.

Bilateral section, as complete as possible, of frontal white matter, in a plane not going posterior to the sphenoidal wings, is most likely to produce pain-relief, is least likely to be followed by relapse with recurrence of symptoms, and is no more probably to be associated with undesirable mental changes than any other modification *which will relieve the pain.* It is of value to start incision anterior to the coronal suture, because postoperative urinary incontinence is minimized.

The temptation to operate upon one frontal lobe only must be guided by reports of relapse of symptoms in a high percentage of cases.[3]

Selection of patients

The family physician, supporting the final illness of a cancer case, is often faced with the problem of obtaining symptomatic treatment when consulting colleagues are unwilling to make further efforts to eradicate underlying pathology. It is in this situation that prefrontal lobotomy is urged as a measure best suited to the over-all management of the case. It may apply equally as well to other painful conditions, where less drastic methods of treatment have proven ineffectual, are precluded on technical grounds, or when the significance of pain as a threat to life is as important to the patient as the pain itself.

A stable female suffering from pelvic carcinoma, with pain in one leg only, ought to be afforded a trial of unilateral chordotomy. Her anxiety-ridden sister, with one severely involved lower extremity, with early symptoms of pain in the other, and with dysuria, is better treated by lobotomy than by bilateral chordotomy.

In further illustration, no one would suggest other than the time-honored procedures of retrogasserian neurotomy or alcohol injection in a case of true trigeminal neuralgia. The atypical case, if severe, will only be relieved by prefrontal operation.[17]

Case-selection may be summarized thus: Lobotomy is superior to other types of interruptive pain-relieving methods when (i) pain-creating pathological foci are multiple and widely disseminated; (ii) probability (as in metastatic carcinoma) exists that new foci will appear later in the course of illness; (iii) pain is bilateral and bladder control should be preserved (versus bilateral chordotomy); (iv) pathological anatomy (as in invasive carcinoma of the floor of the skull) will render selective nerve-section technically hazardous or ineffectual; (v) psychological factors are predominate in the clinical picture, no matter what the source of unrelieved pain; (vi)

addiction to morphine or equivalents seems to be more than simply the natural consequence of seeking relief. This list might be amplified at length, but it is thought to include the most usual indications for performance of prefrontal lobotomy in the pain patient.

Effects of operation

The principal desirable effect of frontal procedure, of whatever type, is relief of pain, or at least of emotional and fear-provoking reactions to pain. This is immediate, and will occur on the operating table. When questioned then or later, the patient indicates an intellectual appreciation or memory of the topic—pain—discussed, without the fervor of gratitude, implying emotional recall of painful memories, seen after successful treatment of sciatica by disc-removal, for example. Or curiosity may be expressed at interrogation; the sensation remains, as such, and the patient is unaware of the radical change in his attitude towards it.

There are certain features of the postoperative state which are common to all lobotomized cases. Inertia, lackadaisical manner, and impulsiveness are such symptoms. An inappropriate or misplaced emotional response is most characteristic of the mental status.[3] Three months may be said to be an average convalescence from the most severe form of the organic confusional syndrome. Since the life of patients dying from carcinoma is often shorter than this, psychic phenomena may persist for the duration of existence.

The principal drawback to the use of lobotomy for relief of pain is abnormal and disagreeable social behavior. Whether or not this is a result of true "personality-change" or simply a revelation of previously suppressed aggressive trends is of academic interest here. It is virtually impossible to predict which patient will make an adequate adjustment after operation and which one will become a behavioral problem. Attempts to evaluate the premorbid personality are hampered by the desire of all concerned to relieve the suffering of the afflicted, and by loyalty and family pride which may give an excellent character sketch of even the most obvious psychopath. The physician should evaluate carefully tendencies to aggression, irritability, and selfishness.

On the other hand, it is reprehensible to frighten a patient or his family away from operation, and there is a serious responsibility incumbent upon those who remain adamant in stating "anything but that." The pain-wracked sufferer is forced to rely upon decreasingly effective injections of opium derivatives during the remainder of his life—which may be longer than anyone would predict—every minute of which may seem as though it were an hour. There are many cases in which lobotomy will answer the patient's prayer, and in which surgery has been prevented by well-meaning but ignorant relatives or physicians, seeking to stave off the knife that "will make him insane."

Operative preparation

The systemic ravages of carcinoma, pathological physiology of drug addiction, and nutritional deficiencies in people suffering from intractable pain tend to make them bad candidates for operation, but they withstand lobotomy surprisingly well. The over-all operative mortality is approximately 8%.

These cases need transfusions of blood, injections of all vitamins, and infusions of protein hydrolysate prior to surgery. A bleeding tendency associated with anemia or simply failure of clotting mechanisms may hamper the surgeon's efforts or result in fatality, a contingency of which the relatives must be apprised. This is "surgery in desperation,"[4] under far from ideal circumstances.

It is fruitless, cruel, and unnecessary to attempt to break the patient of narcotic addiction preoperatively. Postoperatively, care must be used in withdrawing drugs, instead of cutting them off sharply, as has been advocated in some reports.

Complications

The most serious complication of lobotomy for pain is, of course, operative death. Inertia or, more commonly, uncontrolled hemorrhage into the plane of incision accounts for immediate demise. Inspection of postoperative skull films, when lipiodol has been injected, may allow the diagnosis of intracerebral hematoma.[21, 15]

Next most distressing is failure of the "last chance" operation to relieve pain at all, or to produce subsidence of symptoms for a time, only to have them return in full force (see below). Frequent relapse into pain after unilateral lobotomy has been commented upon, but it should be added that more than occasional recurrence of pain follows bilateral operation when the patient lives six months or more. It is conceivable that more radical section (reoperation) might produce the desired effect once more. Ineffectuality of relief at all is rare, and simply means inadequate section of frontal white matter.

The psychic aftermath of lobotomy in the pain-patient may prove to be extremely trying, and requires intensive schooling of the family and attendants. It is of value to emphasize that (i) unpredictable, obnoxious social behavior is not to be tolerated, even though the individual is physically ill, but is to be dealt with firmly, and with respect to the social needs of others; (ii) re-education is helpful, even for so brief a period as the patient's remaining life; (iii) there is less of a personally-directed factor in disturbed conduct than may be apparent.

The most effective attitude in caring for the post-lobotomy pain patient is compounded of equal parts of humorous understanding, firmness with what exceeds the bounds of allowable license, and appreciation of the problems of concern to an individual facing early and invitable death.

Case reports

Typical personal examples of the effect of lobotomy upon intractable pain and upon the patient as a whole may be cited:

Case 1. Thoracic laminectomy was performed upon a 32-year-old female because of epidural Hodgkin's disease. The growth had enveloped the entire cord and its roots. Complaints of burning pain in the trunk and legs, and of knife-like stabs in the shoulders and arms persisted after removal of as much tissue as feasible. Failure of X-ray and nitrogen mustard therapy necessitated lobotomy for pain relief. For eleven months the patient was comfortable, except for abdominal cramps and occasional shooting pains in the left shoulder girdle. She was pleasant, attractive, hopeful, and developed a lucrative cosmetic business. One year postoperatively the original, pervasive pain syndrome recurred and persisted for the brief remainder of her life.

Case 2. Minimal, bilateral lobotomy was undertaken in a 45-year-old female who developed intractable pain in the left shoulder and arm several years after radical mastectomy. Nerve blocks were ineffectual. The patient was taking dilaudid, gr.1/32, every three hours in order to ensure a reasonably comfortable existence. For two and one-half years she has been comfortable, happy, and does not require narcotics. The etiology of pain was indicated clearly when metastases were removed from the opposite breast six months after lobotomy. The patient manages her household and has expressed her gratitude (unusually!) in letters.

Case 3. After ten years of progressive amputation and nerve resection intended to relieve pain in the right arm associated with chronic osteomyelitis, a 61-year-old female was subjected to bilateral lobotomy because of a causalgic, chronically painful phantom limb. Afterwards, she joked about pain in the arm, did not dwell upon the subject as formerly, and was restored to work capacity in her daughter-in-law's home. Death occurred three years later, from coronary thrombosis.

Case 4. A 42-year-old female was reduced to complete incapacitation and dependency upon decreasingly effective hypodermics of pantopon, gr. ½, given every hour, because of agonizing pain in the legs. Malignancy of the breast had spread to the lumbosacral spine. Bilateral lobotomy was performed. The patient went through a stormy time because of withdrawal of narcotics and debility, and then recovered sufficiently to become so vituperative and obscene a virago as to result in discharge from hospital at the request of the nursing staff.

Two months later, she had become a tractable but outspoken member of society, complaining only of acute pain when her knees were manipulated without warning. She expired four months after surgery.

Case 5. Chronic pain in the low back had dogged the existence of a 53-year-old female since the age of 17. She had fractured her coccyx at the age of 9. An attack of typhoid fever at 18 was almost fatal. Intractable pain in the entire spine and both legs had been increasingly severe during the seven years prior to operation, and she had been bedfast and addicted to dilaudid for six months. Roentgenograms of the spine and myelography disclosed arthritis with nerve-root encroachment. There were objective evidences of long-tract cord disease. One could not touch her back or legs without screaming complaints; indeed, she was unable to tolerate the weight of the bed-covers. Bilateral lobotomy (lower quadrants only) resulted in cessation of virtually all remarks regarding pain. She does not actually perform housework, preferring to manage a passive daughter in this respect. Perception is keen and her family can tolerate her outspokeness. She has been followed for three years.

Case 6. The beneficial effects of unilateral, extensive lobotomy in a 60-year-old female suffering from pain in the leg due to spine metastases from a far-advanced

carcinoma of the lung were so striking as to merit brief comment. For one year postoperatively, until her death, the patient required no more than small doses of codeine by mouth for relief, and although bedfast due to eventual paraplegia, her life was a relatively happy one.

Case 7. Invasive carcinoma of the pancreas reduced the existence of a 42-year-old white male to hapless dependence upon morphine-hyoscine mixture which was "like so much water" after three months of two- and three-hourly injection. Bilateral lobotomy was performed through atrophic frontal lobes, with trepidation because of jaundice and low prothrombin levels. Postoperatively, this pillar of society became such a pugnacious practical joker and general social menace as to necessitate firm and abusive talkings-to and the securing of male nursing attendants. Complaints of pain were utilized to plead for mercy *re* the latest escapade. Eventually (one month), the patient regained equilibrium, and psychic abnormality persisted only insofar as to make him the "life of the party." Occasional injections of Demerol were sufficient to control discomfort.

Summary and conclusions

Prefrontal lobotomy offers a distinct assistance in the management of the patient who is wracked with intractable pain due to carcinoma, or other condition in which complaints of pain upon an organic or quasi-organic basis are not relieved by usual conservative or surgical measures. The mechanism of effect is unknown, and may be explained upon neurophysiological as well as psychiatric grounds. Various types of operations upon the frontal lobes have been described and proposed in the pain problem; the original bilateral frontal subcortical sectioning is as effective as any, is less likely to be followed by relapse than are the more conservative variations, and is technically more simple than some. Potentially high surgical mortality may be reduced by consideration of factors of debilitation and tendency to hemorrhage in these patients. Disturbing psychic reactions are usually temporary and controllable, but may be very upsetting and require intensive care and understanding. The family should be informed and instructed. An evaluation should be made of pre-morbid personality makeup as accurately as possible, if only to attempt to prognosticate anti-social activity after operation. Lobotomy does not render the individual pain-insensible, nor does it make him psychotic. The effect of frontal incision is to afford cessation of chronic, pervasive, agonizing pain, with preservation of appreciation of sharp, briefly-acting stimuli. Lobotomy for the relief of pain has withstood the test of time. Typical cases are presented.

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FIBROUS DYSPLASIA OF BONE

Neurosurgical Considerations in Two Cases*

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Fibrous dysplasia is a disease which may be manifested in a single bone as tumefaction or a solitary cyst (monostotic type), in a region involving contiguous bones, or in a diffuse manner (polyostotic type), the latter possibly in association with endocrine and developmental disturbances.

The condition is of interest to the neurological surgeon when the cranial or cranio-facial structures are involved, and often the problem may be one of diagnosis rather than of therapy. Neurosurgical consideration becomes necessary when the cranial involvement simulates the changes often seen in association with a meningioma, or when the progress of the disease produces cranial tumefaction or encroaches upon intracranial structures. The following two cases illustrate these conditions.

Case 1. The patient was a 14-year-old Negro girl admitted to the hospital in December 1950 because of diffuse enlargement of the left frontal region. Very little detailed history could be obtained other than that general enlargement and increasing prominence of the left frontal region and brow had been apparent over a period of at least six months, in association with some mild local discomfort. There was a history of diplopia, but apparently neither the visual disturbance nor the pain had been of sufficient severity to cause any marked discomfort.

The clinical findings were related to the skull. There was bony prominence of the left frontal and frontotemporal region which also involved the outer two-thirds of the supraorbital ridge. The bony lesion extended upwards for a distance of about 4 to 5 cm., and laterally into the temporal region for a similar distance. In the frontotemporal region the prominence was moderately well defined, but the lesion itself was not sharply delineated at any point. There was a suggestive fulness of the left zygomatic region but no apparent involvement of the mastoid area. The left globe appeared to be displaced downward and possibly slightly forward, although extraocular muscle function was grossly normal. The overlying scalp was not unusual and could be moved freely. The neurological examination was otherwise within normal limits.

X-rays disclosed a marked increase in density involving the lower and outer portion of the left frontal bone, the roof of the orbit, and the lateral wall of the orbit, with extension posteriorly to involve the sphenoidal ridge.

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Received for publication April 10, 1951.

In addition to the increased density and increased thickness of the involved bone, there was a vague suggestion of destruction but the X-ray picture was generally one of proliferation rather than destruction (Fig 1A).

During the course of hospitalization, spinal fluid studies were completely normal as was the blood chemistry. The serum alkaline phosphatase was 2-4 units, the blood serology was negative, and the blood count and urinalysis were not unusual.

Despite the fact that there was no clinical evidence of an intracranial space-occupying lesion, pneumoencephalography was carried out to make certain that the bony disturbance did not represent changes secondary to an underlying neoplasm. The pneumoencephalogram was normal with no evidence of displacement or distortion of the ventricular system (Fig 1A).

A clinical diagnosis of fibrous dysplasia of bone was made and biopsy done for confirmation. A 2-cm. circular segment of bone was removed from the left frontoparietal region. The bone, while not unusually vascular, was of increased thickness and was relatively soft. The underlying dura was normal and there was no evidence of a tumor.

The specimen of bone was approximately 1 cm. thick, greyish-white in appearance, and on close inspection had more prominent trabeculation than is usually seen in bone removed from the calvarium. Microscopic examination after decalcification showed the trabeculae to be narrow, small, and quite irregular. The bone spicules had the usual histologic appearance with no calcification and uniform staining quality. The marrow cavity, however, was completely replaced by moderately dense connective tissue which had an interlacing pattern and occasional whorl formation. In many places there was evident penetration of the bony trabeculae by the bundles of connective tissue and collagenous fibers. In many places, at the periphery of the connective tissue bundles, were large multinucleated giant cells. In no place was any of the usual bone marrow element present (Fig. 1B).

Case 2. The patient was a 14-year-old girl who was first seen in February 1950 because of a large tumor on the right side of the head. It had been present for about four years and although there had been slowly progressive enlargement of the tumor mass there had been no tenderness or pain. For about a week prior to examination the patient had experienced some frontal headache.

Examination revealed a well-developed, well-nourished, 14-year-old white girl who did not appear to be ill. There was a large bony mass measuring approximately 7 cm. in diameter occupying the right parietal region and extending close to the midline. The tumor did not pulsate, was not tender, and there was no audible bruit. The lesion was moderately well defined and the overlying scalp did not appear to be involved.

X-ray examination revealed the bony tumor involving the posterior portion of the right parietal bone. The outer table of the skull was irregularly involved but the inner table showed less definite evidence of involvement.

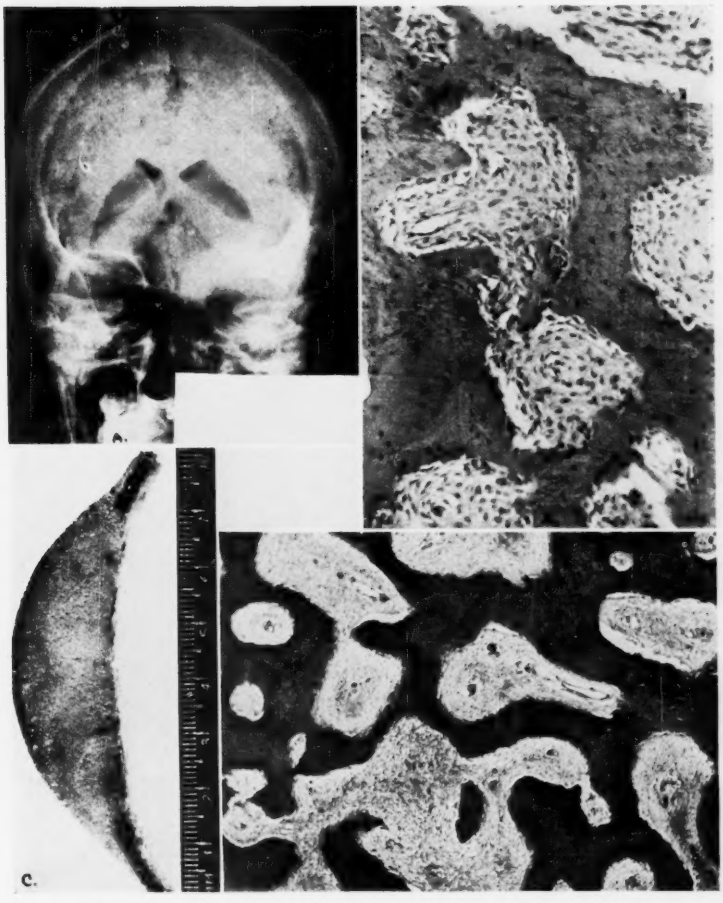

FIG. 1. *Case 1.* A. Pneumoencephalogram showing thickening of sphenoid area and normal ventricular system. B. Photomicrograph of bone removed at operation. Note replacement of marrow by connective tissue. H. & E. x100.

Case 2. C. Cross-section of bony tumor. Note trabeculation of cut surface and absence of diploic space. D. Photomicrograph of tumor. Note trabeculation and replacement of normal marrow by connective tissue. H. & E. x50.

The lesion was of increased density but appeared to be poorly calcified in comparison to the usual bony tumor. The diploic space could not be identified in that region of the skull occupied by the tumor.

The remainder of the examination was within normal limits.

Spinal fluid studies were normal. The blood serology was negative and there was no abnormality in the blood count or urine examination. At operation the bony lesion was exposed by a circular flap with the base above the mastoid region. The scalp was quite vascular and there was considerable bleeding from the surface of the bony tumor which was smooth but not shiny, had a dusky pink color, and which appeared to be rather sharply demarcated from the surrounding bone only by the difference in color. A single trephine opening was made at the anterior edge of the tumor mass and the entire lesion removed by encircling it with the biting rongeurs. The bone was extremely vascular and where the edge of the tumor was included in the removal, very active bleeding occurred from the tumor edge. The tumor was much softer than normal bone. The exposed dura was not unusual and there was nothing to indicate any involvement of the dura or underlying structures. A tantalum plate was fashioned to cover the defect.

The postoperative course was complicated by the development of an extradural hematoma which required re-exploration of the wound on the third postoperative day. This was associated with a mild right hemiparesis which had almost completely subsided at the time of hospital discharge and which had recovered completely within a period of four months.

Microscopic examinations after decalcification showed the typical appearance of fibrous dysplasia of bone with narrow irregular bony trabeculae and replacement of marrow elements by mature fibrous connective tissue and collagenous bundles (Fig. 1D).

Discussion

Involvement of the calvarium by the monostotic form of fibrous dysplasia is unusual although Schlumberger[4] reported 5 of 67 cases involving the calvarium. In rare instances the lesion may be cystic, as was recently reported by Paget and his associates.[3]

Of particular interest in the first case was the manner in which the disease simulated the changes frequently seen in meningioma of the sphenoidal ridge or of the so-called *"meningioma en plaque."* The problem was one of diagnosis rather than therapy at the time the patient was seen, since with extensive regional involvement such as was present, complete excision of the involved area could not be carried out. However, further encroachment upon the orbit with subsequent displacement of the globe may eventually occur if the lesion continues to progress, and may require orbital decompression.

In the second case the character of the tumor was unlike that seen in involvement of bone by a meningioma although this possibly could not be completely excluded upon the basis of the radiological examination. Excision of the lesion should result in a cure, and it seems unlikely that the disturbance will appear elsewhere in the polyostotic form.

In the monostotic form the local lesion grows slowly or may even remain stationary once it is manifested clinically. It is not associated with the endocrine disturbances or congenital anomalies described by Albright,[1] and the complete removal of the local lesion, when possible, usually gives a satisfactory result. The pathological process appears to be a true dystrophic change in which normal ossification is inhibited or completely prevented. The disturbance is essentially a benign one, although some cases of sarcomatous change developing in areas of fibrous dysplasia have been reported.[2]

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STUDIES ON THE METABOLISM OF CARDIAC MUSCLE FROM ANIMALS IN SHOCK*

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In previous studies it has been shown that the oxygen consumption of cardiac muscle is altered in both hemorrhagic and traumatic shock. Originally, slices of muscle were taken from rats in the terminal stages of hemorrhagic shock,[4] and it was found that there is a depression of Q_{O_2} in the samples from the treated animals. This was repeated,[8] using hearts from animals killed at intervals after treatment (bleeding or the release of tourniquets applied to the hind legs). It was discovered that at first there is an elevated oxygen consumption followed by a significant decrease below normal levels about the fourth hour. Later there is a secondary rise in Q_{O_2}. These relative changes occur both with and without the addition of sodium pyruvate substrate, although the oxygen uptake is higher when pyruvate is present.

The present report outlines the results obtained in experiments continuing the study of changes occurring in cardiac muscle in animals following hemorrhage and the release of constrictors. Determinations of glycogen, lactic acid, and pyruvic acid content of cardiac muscle have been made before and after treatment. It has also been possible to determine the respiratory quotient for the tissue. It is well known that serum potassium levels are quite high in the later phases of shock, and because of the importance of this ion in the metabolism of cardiac tissue, there is the possibility that an increased concentration of potassium might be responsible, at least in part, for the alterations in the metabolism of the muscle shown to be present. In order to test this, potassium was reduced in the saline solution in Warburg vessels and oxygen consumption was determined. The effect of sodium iodoacetate on oxygen consumption of control and experimental groups was also tested.

Methods†

Shock was induced by the application of rubber bands to the hind legs followed by release,[20] and also by bleeding from the tail vein over a period of one hour by the method of Sayers, Sayers, and Long.[30] The latter method was used in only a few determinations. Rats used were fasted for 24 hours but allowed free access to water. The heart was quickly removed, slices cut 0.5 mm. in thickness, and vessels containing

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† The valuable technical assistance of Mr. Bryan Harwell in the course of this study is acknowledged.

Received for publication April 17, 1951.

the tissue kept on ice. Oxygen consumption of the slices was determined at 37.5° C. by the direct method of Warburg with gas phase of 100% oxygen. Substrates were added at zero time from the side arm. The respective final concentrations in separate experiments were as follows: 0.02 M sodium pyruvate, 1.0 mM glucose, 0.02 M sodium lactate, 0.02 M and 0.002 M beta-hydroxybutyric acid, and 0.25 mM sodium iodoacetate. The saline medium used was Krebs-Henseleit solution buffered with phosphate containing 2.5 mEq. of calcium per liter. The concentration of potassium was reduced from 5.0 mM to 0.4 mM in testing the effect of reduced potassium concentration on the oxygen consumption of cardiac muscle from shocked rats. Bicarbonate buffer was substituted for the measurements of respiratory quotient and glycolysis. The second method of Dickens and Simer[11] was utilized for determining respiratory quotient and glycolysis, using modified Dixon-Keilin vessels. Glycogen was determined in the manner reported by Good, Kramer, and Somogyi,[17] lactic acid as reported by Barker and Summerson,[1] and pyruvic acid by the method of Friedemann and Haugen.[15]

Results

An average of 1.78 ml. of blood per 100 square cm. surface area was removed from the animals which were bled. Most of the animals studied

TABLE 1

OXYGEN CONSUMPTION OF CARDIAC MUSCLE IN MEDIUM OF REDUCED POTASSIUM CONCENTRATION

Tourniquet	*Time after release*	K	*No. of determinations*	*30 Minutes* Mean Q_{O_2}¶	P	*60 Minutes* Mean Q_{O_2}	P	*90 Minutes* Mean Q_{O_2}	P
Control		+*	6	4.19±0.70‡		3.35±0.43		3.43±0.48	
Control		0†	3	3.62±0.80		3.28±0.28		2.86±0.72	
3 hr.	6 hr.	+	14	6.64±0.57	0.04	6.51±0.61	0.01	6.12±0.51	0.01
3 hr.	6 hr.	0	7	7.12±0.94	0.08	5.72±0.53	0.03	5.68±0.82	0.09
5 hr.	1 hr.	+	10	5.34±0.22	0.01	5.23±0.11	0.01	5.19±0.09	0.01
5 hr.	1 hr.	0	5	6.18±0.18	0.01	5.56±0.08	0.01	5.45±0.12	0.01
5 hr.	2 hr.	+	16	4.54±0.65	0.8	3.80±0.70	0.8	3.87±0.51	0.6
5 hr.	2 hr.	0	8	5.16±0.96	0.4	4.46±0.69	0.4	3.52±0.62	0.3
5 hr.	4 hr.	+	8	2.97±0.49	0.2	2.36±0.42	0.2	1.97±0.40	0.05
5 hr.	4 hr.	0	4	2.03±0.49	0.2	1.31±0.39	0.02	1.48±0.41	0.2

* 5.0 mM K.
† 0.4 mM K.
‡ Standard error of the mean.
¶ Cu. mm. of oxygen consumed per mg. of initial dry weight per hour.

were treated by application of rubber bands to the hind limbs with release subsequently, and this proved to be a more satisfactory method of producing shock than hemorrhage. None of the rats was anesthetized. In previous work[3] it was found that both of these methods of inducing shock are sufficiently effective to result in elevation of amino acid nitrogen levels in the serum.

When the concentration of potassium is lowered in the medium it is

evident that early in shock the oxygen consumption is raised, subsequently it falls below normal levels, and later there is a secondary rise presumably with recovery (Table 1), although not all of the differences are significant. When the potassium is reduced in the medium, in slices respiring at a lowered rate (four hours after release of a tourniquet which had been in place five hours), the average Q_{O_2} is lowered for every time interval, although the difference is of questionable significance. The mean values for oxygen uptake in Table 1 are not uniformly elevated nor depressed in the presence of reduced concentration of potassium.

The average glycogen content, expressed as mg. glucose per 100 g. of tissue, decreased from 450±21 mg. to 338±50 mg. two hours following hemorrhage and to 395±47 mg. three hours after bleeding (Table 2). A corresponding diminution in glycogen content occurred in the gastrocnemius. The reliability of this trend is limited by the extreme variability

TABLE 2

GLYCOGEN DETERMINATIONS FOLLOWING HEMORRHAGE

Time following hemorrhage	*No. of determinations*	*Heart*	*Gastrocnemius*
Control	19	450±21	473±49
2 hr.	8	338±50	
3 hr.	16	395±47	429±28

in the values obtained in the different specimens. This decrease in glycogen content is significant and more convincing for cardiac muscle obtained from animals treated by application of tourniquets and subsequent release. Four hours after release of constrictors applied for three hours the glycogen content was 182±18 mg. in contrast to average control values of 362±12 mg. When tourniquets were applied for five hours there was little change at the end of two hours at which time the average glycogen content was 329±32 mg., but four hours after release, average glycogen values were 178±22 mg.

The average level of pyruvic acid (expressed as mg. per g. of tissue) in cardiac muscle from control animals was 0.017±.001 mg. (Table 3). Four hours after release of constrictors it was 0.028±.003 mg. in those applied for three hours and 0.038±.003 mg. in those applied five hours. In the group with rubber bands applied five hours there was 0.030±.003 mg. of pyruvic acid per mg. of muscle two hours after release.

The average lactic acid content was found to be 0.075±.004 mg. per gm. of tissue from those animals not treated and 0.137±.018 mg. from those treated by application of constrictors three hours and killed four hours after

release (Table 3). This elevation in average lactic acid content is less evident in those animals treated by application of the tourniquet for five hours and sacrificed two and four hours after release of the constrictors respectively. These average values are 0.069±.006 mg. and 0.088±.014 mg. respectively, and the difference between them and control values is not significant.

TABLE 3

GLYCOGEN, LACTIC ACID, AND PYRUVIC ACID CONTENT OF CARDIAC MUSCLE IN SHOCK

Tourniquet	*Hr. after release*	*No. of determinations*	*Glycogen mg. glucose per 100 gm. tissue*	*No. of determinations*	*Lactic acid (mg./gm.)*	*No. of determinations*	*Pyruvic acid (mg./gm.)*
Control		10	362±12	15	0.075±.004	15	0.017±.001
3	4	8	182±18	15	0.137±.018	15	0.028±.003
5	2	5	329±32	10	0.069±.006	10	0.030±.003
5	4	7	178±22	10	0.088±.014	10	0.038±.003

TABLE 4

EFFECT OF SODIUM IODOACETATE ON OXYGEN CONSUMPTION OF CARDIAC MUSCLE 4 HOURS AFTER RELEASE OF TOURNIQUET

Tourniquet	*Iodoacetate*	*No. of determinations*	*30 Minutes* Mean Q_{O_2}	P	*60 Minutes* Mean Q_{O_2}	P	*90 Minutes* Mean Q_{O_2}	P
Control	0	8	2.14±0.41		1.68±0.36		1.08±0.15	
Control	+	8	1.59±0.29		1.22±0.24		0.27±0.06	
3 hr.	0	8	2.02±0.12	0.80	1.11±0.18	0.2	1.17±0.18	0.70
3 hr.	+	8	1.53±0.38	0.90	0.69±0.09	0.1	0.71±0.07	0.001
5 hr.	0	8	1.15±0.22	0.08	1.09±0.11	0.2	0.83±0.09	0.30
5 hr.	+	8	0.76±0.18	0.046	0.81±0.08	0.2	0.65±0.12	0.028

The presence of 0.25 mM sodium iodoacetate in the medium is associated with a diminution in oxygen consumption of slices of cardiac muscle both from control and treated animals (Table 4). There is no significant difference between the average Q_{O_2} determinations for control and treated groups in the absence of iodoacetate. There is a significant difference between the control and treated groups with added iodoacetate in half of the six intervals recorded in the Table 4. However, for two of the intervals (the three- and five-hour application of constrictors during the 90-minute interval), the oxygen consumption is higher than the control, whereas it is lower for the remaining interval (the five-hour group during the 30-minute interval).

The mean respiratory quotient was found to be 0.76 for the slices from rats without treatment and 0.71 for the tissue from treated rats (Table 5). The amount of glycolysis calculated from the same data was found to be 15.7 (expressed as X_0) in the control group and 24.8 in the treated group. The results of preliminary work on the effect of adding glucose, sodium lactate, and beta-hydroxybutyric acid are also presented in Table 5.

TABLE 5

RESPIRATORY QUOTIENT AND GLYCOLYSIS OF CARDIAC MUSCLE IN SHOCK

*Treatment**	*Substrate*	*No. of determinations*	*Mean R.Q.*	*No. of determinations*	*Mean* X_0
0	0	9	0.76±0.16	9	15.7±3.8
+	0	8	0.71±0.004	8	24.8±4.2
0	0	2	0.78	2	27.9
0	Glucose	3	0.66	3	57.08
+	0	2	0.68	2	11.9
+	Glucose	2	1.09	2	17.6
0	0	2	0.59	2	21.5
0	Sodium lactate	2	0.94	2	0.0
+	0	2	0.84	2	18.8
+	Sodium lactate	2	0.85	2	12.2
0	0	3	0.80	3	14.5
0	β-hydroxybutyric acid	3	0.89	3	21.8
+	0	3	0.77	3	25.5
+	β-hydroxybutyric acid	3	0.84	3	22.6

* Animals killed four hours after release of constrictors which had been applied twelve hours.

Discussion

There is some evidence that the state of the myocardium is a factor in determining the outcome of the shocked state. It is more difficult to assign a time at which significant alterations occur, but it is probably late. Previous work[3] on oxygen consumption of cardiac muscle from animals in shock has already been mentioned. Wiggers and Werle[33] have reported that the response of the ventricles to any given venous pressure is impaired in hemorrhagic shock in dogs and feel that this is one of the precipitating causes of irreversible shock, although it may not be evident when the venous pressure is declining concurrently. Kohlstaedt and Page[23] noted that progressive increase in size of the canine heart following a sharp increase in venous pressure as a result of prolonged hypotension was an invariable omen of the terminal, irreversible phase of hemorrhagic shock. The size of

the heart is smaller earlier in shock.[25] Furchgott and Shorr[24] found a lower rate of turnover of high-energy phosphate compounds in slices of cardiac muscle from animals in shock. The studies of LePage[25, 26] indicate that the heart shows signs of stress in shock but possesses energy reservoirs in excess of brain, kidney, and liver. Certainly the metabolic changes in the heart cannot be considered apart from those in other tissues.

The resistance of the heart to depletion of stored energy depends in general on capacity for anaerobic glycolysis, reserves of phosphate-bond energy, and impairment of circulation and oxygen supply.[24] It is reasonable to suspect that anoxia may account for much of the effect of shock on the myocardium. The cardiac output, stroke volume, and the coronary flow are diminished in hemorrhagic shock. It has been pointed out by Eckenhoff and coworkers[13] that rate of oxygen consumption by cardiac muscle is dependent on coronary flow, which in turn depends on blood pressure. Fuhrman, *et al.*,[16] found that oxygen consumption of cardiac muscle was reduced 35% in rats exposed to progressively decreasing atmospheric pressures until death occurred. It has been shown by Clark and associates[6] that the frog's heart can maintain activity under anaerobic conditions by glycolysis, which is limited by the supply of carbohydrate and alkalinity of the perfusion fluid. However, the mammalian heart is more restricted in its ability to function anaerobically.

With anoxemia such as that produced by Himwich, Goldfarb, and Nahum[19] by ligating the coronary vessels, glycogen is lost from the infarcted areas. Diminution of cardiac glycogen was demonstrated in shock by LePage.[25] Goranson, Hamilton, and Haist[15] have shown that there is also a reduction in glycogen concentration in uninjured skeletal muscle from rats shocked by a clamping technique. This was not prevented by administration of insulin, and they suggest this may be initiated by poor oxygen supply to these tissues. In this study there was decreased glycogen content in both hemorrhagic and traumatic shock (Table 2), but the results in the former are equivocal for both cardiac and skeletal muscle. At the end of four hours following release of tourniquets there is a significant decrease in the amount of glycogen in cardiac muscle (Table 3). This change occurs at the time there is a fall in oxygen consumption of this tissue,[3] and it may be associated with anoxia.

Cardiac muscle utilizes lactic acid,[5, 27] and in certain circumstances such as those found in the failing heart-lung preparation, diabetes, and the heart poisoned with iodoacetic acid in the presence of oxygen, lactic acid is utilized even though the ability to utilize glucose is limited or absent. With anoxemia, lactic acid is no longer removed from the blood, but is produced and added to the circulation.[5] When the glycogen stores are exhausted, the production of lactic acid ceases. In the present studies the lactic acid content of the muscle is significantly higher in one of the treated groups (Table 3), and this change may possibly be due to a diminishing supply of oxygen.

Similar change in the lactic acid content in shock has been reported by LePage.[25, 26]

Pyruvic acid is significantly elevated in hearts from animals in shock (Table 3). This accumulation of pyruvic acid may mean that the degree of anoxia present in shock interferes with the breakdown of carbohydrate through the tricarboxylic acid cycle. It should be remembered that addition of pyruvate results in an elevation of depressed Q_{O_2} of slices from animals in shock although not to the extent of those with available pyruvate in control experiments.[3, 4] In shock, levels of pyruvate and lactate are also elevated in the blood with relatively greater increase in lactate[9, 13] in the later stages.

Although glucose is believed to be the source of cardiac glycogen, glucose absorption by the functioning heart has been reported as minimal or absent by some investigators.[7, 27] However, the synthesis of glycogen by rat cardiac muscle slices was logarithmically related to glucose concentration in experiments by Stadie, Haugaard, and Perlmutter.[21] Addition of glucose to slices from both control and shocked animals is associated with increased glycolysis (Table 5). The R.Q. is elevated after addition of glucose only in the shocked group. On the other hand, lactic acid is associated with a higher R.Q. in the untreated group only. There is some indication, therefore, that the utilization of glucose is increased and that of lactic acid is decreased in shock.

The mammalian heart is capable of non-carbohydrate metabolism as well as almost pure carbohydrate metabolism.[5, 24, 27] This is evident from determinations of R.Q. in isolated preparations and catheterization studies, studies on oxidation of fatty acids *in vitro*, survival of the muscle for some time without carbohydrate, and calculation of oxygen required for oxidation of lactic acid and glucose. The low R.Q. values in Table 5 suggest that material other than, or in addition to, carbohydrate is being utilized by the slices in saline medium. There is no significant difference between the R.Q. of the muscle from rats in shock and those without treatment. Glycolysis is higher for samples from the treated group, but the figures are of marginal significance. Addition of beta-hydroxybutyric acid did not lower R.Q. in either of the two concentrations used. Conclusions based on R.Q. values, particularly those where the number of determinations is small, are viewed with some reservation and are considered preliminary in nature.

It is evident in Table 4 that sodium iodoacetate has caused a decrease in average Q_{O_2} of slices from rats in shock as well as those without treatment. The oxygen consumption is quite low in the muscle which has not been poisoned with iodoacetate, and the difference in oxygen consumption between samples from treated and control groups which previously has been demonstrated is not evident in these data. It is clear, however, that the systems affected by the iodoacetate are still functioning at least partially in shock.

The toxic effect of high concentrations of potassium on the heart[25] is well known. Hemorrhagic and traumatic shock may be associated with an increase in potassium concentration in the blood,[9] which is probably most consistently a terminal event.[20] In advanced circulatory failure due to hemorrhage and trauma, Davis[9] found that smaller amounts of potassium were required to produce the toxic effects of this ion and that death was hastened by the increase in potassium concentration. Asphyxia may also result in elevated blood potassium levels,[10] perhaps largely mediated through the liberation of epinephrine and release of potassium from the liver,[21] although Fenn[14] has reported that asphyxia can cause loss of potassium from various tissues besides the liver. In contrast to the findings in asphyxia, McQuarrie and associates[20] found lower levels of potassium in dogs breathing an atmosphere with reduced oxygen tension for several hours. Omission of potassium alone from the medium caused no change in the respiration of slices of cardiac muscle in the experiments of Bernheim and Bernheim,[3] but decreased concentrations of the ion resulted in a lowered initial rate of respiration in the studies of Webb, Saunders, and Thienes.[22]

There is no consistent effect of reducing the potassium concentration on oxygen consumption of the slices when both experimental and control data are examined (Table 1). Treatment resulted in diminished Q_{O_2} in only one group (four hours after release of constrictors applied five hours). When the Q_{O_2} values for samples from this group were measured in a medium with reduced potassium, still lower oxygen consumption was found. If the lower Q_{O_2} in shock were due to a high level of potassium, the Q_{O_2} should have been elevated in the presence of a medium with reduced potassium, which is not the case. It therefore appears unlikely that the effect of shock on oxygen consumption of cardiac muscle is due to elevated levels of potassium in the blood.

It is apparent from these comments that there are certain changes in the metabolism of cardiac muscle in the shocked state. An increase in oxygen consumption and pyruvic acid content may occur early, and later there is a decrease in glycogen stores and Q_{O_2} and an increase in lactic acid content. Oxygen consumption may still be inhibited by iodoacetate, and depressed Q_{O_2} may be elevated by addition of pyruvate. Determinations of R.Q. indicate that other material as well as carbohydrate may be utilized in shock. The changes found could be explained by the effects of reduced oxygen supply on the muscle. However, some caution should be exercised in reaching the conclusion that anoxia is entirely responsible for the effects of shock on the heart, since it is known that the effects of anoxia differ from those of shock on pulse, arterial and venous pressure, cardiac output, etc.[9] Undoubtedly shock may affect the metabolism of cardiac muscle profoundly, particularly in the later stages, but as a tissue it is not so greatly affected in many respects as the tissue of certain other organs.[25, 26, 24] Whether impair-

ment of its function as the central organ for maintaining the circulation minimizes the importance of these differences is not clear at the present time, and the feasibility of improving the entire circulatory picture by correcting defects produced by shock is a subject for continued study.

Conclusions

1. The glycogen content of cardiac muscle from fasted rats was decreased in traumatic shock.

2. The pyruvic acid content and, at times, the lactic acid content of this tissue were increased in traumatic shock.

3. Reducing the potassium concentration in the medium to offset the elevation in serum potassium levels late in shock did not abolish the effect of shock on the Q_{O_2} of muscle slices.

4. Sodium iodoacetate depressed the oxygen consumption of cardiac tissue from animals in shock.

5. The average R.Q. of cardiac muscle slices respiring in saline medium was 0.76 for animals without treatment and 0.71 for animals in shock.

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THE PRESENT STATUS OF TOCOPHEROL AND CALCIUM FOR PROPHYLAXIS OF POSTOPERATIVE PHLEBOTHROMBOSIS*

JOHN H. KAY**

Since the publication of the early *in vitro* experiments with tocopherol,[2, 4] I have published, with others, reports on the clinical use of what we have called an antithrombin test and on the use of tocopherol and calcium as prophylactic agents in postoperative thrombosis.[3, 5] Since we originally had no concept of the course the clinical work would follow, certain statements which are contradictory appear in these earlier articles as they are read in chronological order. It is the purpose of this article to clarify certain of these statements and to attempt to define the phenomenon which we measure by the antithrombin test.

In the evaluation of any work, it seems reasonable that it should be broken down into its component parts and that these should be evaluated separately before the whole is accepted or discarded. Our clinical work on phlebothrombosis has consisted of three parts. One part is the evaluation of the antithrombin test as an indicator of a prethrombotic state. The second part concerns the effect of alpha tocopherol and calcium on antithrombin levels. The third part concerns the effect of alpha tocopherol and calcium on the incidence of intravascular clotting. Our data will be considered from these three aspects.

Certain basic data must be mentioned before the antithrombin test which we have devised is described. In our first paper on the ability of alpha tocopherol to inhibit thrombin, the statement was made that "practically no antithrombic activity remains in the supernatant fluid" after precipitation of the disodium salt of alpha tocopherol (25 mg.) by 0.1 ml. of 1 per cent $CaCl_2$. Subsequently we published studies on the use of calcium and tocopherol to increase the ability of plasma to inhibit thrombin. In our *in vitro* work in which we were dealing with thrombin in amounts of from 2 to 150 units, we found that the calcium salt of alpha tocopherol is only able to inhibit 0.06 units of thrombin. However, in dealing with plasma, we found that it requires only 0.06 units of thrombin to produce clotting in all normal plasmas. An amount of inhibitor which can be regarded as practically none in the first instance thus becomes of great significance when one is dealing with plasma.

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* From the Department of Surgery, Tulane University School of Medicine, New Orleans. This investigation was supported in part by a research grant from the National Institutes of Health, U.S. Public Health Service and in part by a research grant from the Warren-Teed Products Co.

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Received for publication April 17, 1951.

It should be emphasized again that there is a 1:1 relationship between the concentration of fibrinogen and the antithrombic activity of the sodium salts of alpha tocopherol. Thus it is necessary to add 5 mg. of the disodium salt of alpha tocopherol to plasma before a measurable increase in the ability of plasma to inhibit thrombin is noted. On the other hand, mere traces of the calcium salt of alpha tocopherol raise the level of plasma to maximum normal levels.

Further misunderstanding (which I did not anticipate) has arisen from an attempt by some observers to carry over the *in vitro* work to the *in vivo* interpretation of these phenomena. This is not justified. In working with the alpha globulin thrombin inhibitor we were able to identify a tocopherol-like molecule. This compound was assayable by the Emmerie-Engle technique. It should be remembered that the phosphate salt of alpha tocopherol is not assayable by this technique, it being the=OH radical of the quinone portion of the molecule which is responsible for the anti-oxidant action of the molecule in this reaction.

We do believe that the antithrombic activity of this fraction is due to its tocopherol content, since we have tested other salts (alpha tocopherol sulphate and chroman, and coumarin phosphate)* and have found that the only effective thrombin inhibitors are those with the full tocopherol structure. These observations led us to conclude that it is the structure of the molecule, rather than any specific chemical reaction, which accounts for its activity, and to conclude further that if the molecule could be made water-soluble in the form of a lipo-protein, it would retain this activity.

This will mean, however, that assayable levels of alpha tocopherol will not appear in circulating blood following the administration of alpha tocopherol phosphate unless the tocopherol is hydrolyzed before or after venous blood is withdrawn. The former is apparently not the case.

The data do not justify the conclusion that alpha tocopherol phosphate is a normal constituent of blood or that the antithrombic effect of the administration of alpha tocopherol phosphate reproduces a normal physiological metabolic process. Epstein and Morgulis,[1] however, have published data on the efficacy of alpha tocopherol phosphate in treating nutritional muscular dystrophy in rabbits, which means that the avitaminosis responds to therapy with tocopherol phosphate.

Further confusion concerning our work has arisen from the fact that the antithrombin test is not entirely reliable when a commercial source of thrombin is used. In our original work we used 65 unit-ampules of thrombin, which were carefully assayed. Using this particular source of thrombin, we described a one-stage and a two-stage technique, the two tests correlating well. When, however, we began to use a commercial thrombin, which is the only source available to most investigators, we found that the one-stage technique, which we had reported in two published articles, was un-

*Supplied by Mr. Rudolph Frundt of the Warren-Teed Products Co.

satisfactory and that the two tests no longer correlated, low values being obtained more frequently with the two-stage. Above 1 : 16 the correlation was very good, but 1 : 8 levels were seldom obtained with the one-stage technique, while they continued to occur when the two-stage technique was used. The difference between the two tests is fairly simple. In the one-stage technique, the clot is read after the thrombin is diluted and added to whole plasma. In the two-stage technique, the plasma is diluted, a constant amount of thrombin is added, the mixture is incubated, and fibrinogen is added to it before the clot is read. Since amounts of thrombin in the two tests are essentially equivalent, the fact that they do not correlate in low levels immediately raises the question whether we are actually measuring an antithrombin. For this reason, we are now proposing the name "prethrombotic index" for the test which we have described. The thrombin preparations, of course, contain various amounts of the factors necessary to convert prothrombin to thrombin since the technique of preparing thrombin consists of adsorption of prothrombin from plasma and subsequent conversion, by the addition of calcium, thromboplastin, and greater or lesser amounts of accelerator globulin. If the two tests correlated, it would be reasonable to assume that the thrombin is the substance responsible for the clot production. Since they do not, the question arises whether in the two-stage technique we are not measuring the ability of lesser amounts of thromboplastin, calcium, accelerator globulin, or thrombin to convert the prothrombin in diluted plasma. At the present time we are unable to define the exact nature of the test which we use, and we therefore feel that it would be better to call it a prethrombotic index and to emphasize that if the test is to be used for prediction of a prethrombotic stage, it must be done in two stages, as follows:

1. Place in a test tube 1.4 ml. of 1.85% solution of K_2CrO_4.
2. Add 10 ml. of blood as soon as it is withdrawn and mix well.
3. Centrifuge at 1,500 RPM for 10 minutes.
4. Remove the supernatant plasma.
5. Make a serial dilution of the plasma, as follows:
   a. Place 10 tubes in rack; add 0.5 cc. distilled H_2O to all except #1.
   b. Place 0.5 ml. of plasma in tube #1 (1:1).
   c. Place 0.5 ml. of plasma in tube #2 and mix well (1:2).
   d. Place 0.5 ml. of the mixture from tube #2 in tube #3, and mix well (1:4).
   e. Continue to dilute the plasma in the manner described until 10 tubes have been prepared. The dilution in the tenth tube is 1:512.
6. Add to each tube exactly 0.1 ml. of thrombin solution in distilled water. This thrombin is put up in ampoules of varying concentration. Exact amount in each ampoule (labelled 1000 units) can be determined by writing Eugene Loomis, Parke Davis Research Laboratory, Detroit. It is diluted so that each cubic centimeter contains 0.01 unit of thrombin.
7. Shake the tubes well, then incubate them in a water bath at 37.5° C.
8. Add to each tube 0.1 ml. of 3% bovine fibrinogen (Armour and Co.) solution (in distilled water). The fibrinogen must be frozen and thawed. The profibrin which is precipitated by freezing is removed by centrifugation and discarded.

Only the clear supernatant is used. The solution is prepared by weight and contains 40-50% sodium citrate.

9. Incubate the tubes for another 60 minutes.
10. Observe each tube for the last trace of fibrin formation, recording the greatest dilution at which it ceases to occur. The fibrin frequently appears as a fine precipitate occurring in decreasing amounts.
    In normal plasma, fibrin formation ceases to occur when the plasma dilution is between 1:32 and 1:128.

Evaluation of results

The data accumulated over the past two years, we believe, strongly suggest that the test which we have devised actually is of value in predicting thrombosis. Thus in 246 cases that were studied as controls, there occurred 23 cases of thrombosis or embolism, with 5 embolic deaths. All 5 patients showed a 1:8 level on or shortly before the day of death. In one non-fatal instance of embolism, the 1:8 level was not obtained, this being the only case in our control series in which a 1:8 level was not present when either thrombosis or symptoms of emboli developed. Thrombosis was diagnosed clinically in 16 cases in the series. All of these patients were submitted to venous ligation following the diagnosis and in 8 instances, clots were found at the time of the ligation. The diagnosis of phlebothrombosis in these cases was made on the basis of any two of three physical findings, namely, calf tenderness, unilateral edema, or dilation of the peripheral veins. Patients showing only one of this triad were not considered as having phlebothrombosis in this particular portion of study.

Later we broadened these criteria. In the total series of 246 cases, a number of 1:8 levels were obtained in patients who did not develop clinical phlebothrombosis by our criteria of diagnosis. When the prothrombin times were analyzed in relation to the occurrence of 1:8 levels, it was found that only those patients who had normal or near-normal prothrombin times, develop the clinical syndrome.

Our studies indicated that this differential in prothrombin times could not be picked up if rabbit brain thromboplastin was used. When we used thromboplastin from this source, which gives a very rapid prothrombin time, a large percentage of the measurements were found to be normal or 100 per cent. When, on the other hand, a lung thromboplastin was used, which gave a normal control prothrombin time of approximately 16 seconds, it was found that many of the patients showed prothrombin times of over 20 seconds.

In the group of patients showing 1:8 levels and prothrombin times longer than 20 seconds, there was only one instance of thrombosis, a fatal case of cerebral thrombosis confirmed at autopsy. On the other hand, in the group of patients showing 1:8 levels and having prothrombin times shorter than 20 seconds on the same day, 23 developed phlebothrombosis. There was no particular day, in terms of postoperative days, on which the low levels occurred, but it was observed that they usually preceded the occurrence of

clinical symptoms of phlebothrombosis by 6 to 72 hours. Frequently, the clinical syndrome had developed between the time the blood was drawn, the levels determined, and the patients checked on the wards for possible symptoms.

For this chronologic reason the prethrombotic index alone is not entirely practical. Therapy cannot always be instituted before the disease occurs. The test did, however, help us in this particular group of patients in that we were able to ligate their veins perhaps somewhat earlier than would have been possible had we not had information indicating the possibility of thrombosis.

It must further be emphasized that this test must be run every day, including Sunday, since the omission of even one day could mean that the low level on that particular patient might be missed and the prethrombotic state not recognized.

Our experiences with this test have thus led us to place considerable faith in it for predicting the occurrence of thrombosis in association with a low prethrombotic index.

Interpretation of the effect of tocopherol and calcium on the incidence of low prethrombotic index level

The next question of interpretation is concerned with the effect of alpha tocopherol and calcium administration on the prevention of low prethrombotic index levels. Our therapy consists in the administration of alpha tocopherol phosphate in doses of 100 mg. every 8 hours until the patient can take oral medication. After this time, 200 IU of alpha tocopherol acetate are given daily by mouth. In addition, 10 cc. of calcium gluconate are given every 24 hours. Medication is begun immediately after operation.

In 457 patients treated by this routine, we have found only 15 with 1 : 8 levels. Statistically, no further comment seems needed. It is obvious that the administration of tocopherol and calcium, routinely, to postoperative patients results in a marked reduction of the incidence of low prethrombotic index levels. The natural corollary is that if we believe the prethrombotic index to be an efficient method of predicting thrombosis, and if we can maintain the prethrombotic index above that certain low level which is associated with thrombosis, then we should reduce the incidence of thrombosis.

This brings us to the third aspect of our work, namely, the effect of tocopherol and calcium on the incidence of thrombosis. To date we have treated only 457 patients. In evaluating the incidence of thrombosis in so small a group, it is impossible to say statistically that we have influenced the incidence of the disease because of the great variations which are seen from year to year. Our data show that we have had only 15 with 1 : 8 levels and that these have been associated with 5 phlebothromboses, and with two pulmonary emboli. At the present time we consider a patient to have

phlebothrombosis if he presents only one of the criteria which we use for diagnosis. That is, if a patient has only edema, or dilated peripheral veins, or calf tenderness, vein ligation is performed and he is considered to have had a phlebothrombosis. Indeed, at the present time it is our tendency to perform venous ligation on all 1:8 levels if they have any complaint at all referable to the leg. Any conclusion, however, concerning the effect of tocopherol and calcium on the incidence of thrombosis must await a larger series of cases either from our own clinic or from other sources.

TABLE 1

TYPE OF PROCEDURE

	Untreated control cases			*Treated cases*		
	Number	*Thrombo-embolism cases*	*Embolic deaths*	*Number*	*Thrombo-embolism cases*	*Embolic deaths*
Biliary tract	51	5	1	88	1	
Alimentary tract						
Esophageal resection	3			2		
Gastric resection	37	4		69		
Intestinal resection	38	5		74	1	
Closure G1 perforation	9			35	2	1 contributory
Chest						
Pneumonectomy	22	3	2	22	1	1
Lobectomy	10			24		
Chest-Exploratory						
Non-malignant diseases	12	1	1	11		
Malignant diseases	6			12		
Abdomen-Exploratory						
Non-malignant diseases	26			27		
Malignant diseases	16	1	1	21		
Other	18	3*		10		
	246	23 (8 clots)	5	395	5 (no clots)	2

* Following radical neck dissection, endaneurysmorrhaphy, and sympathectomy.

Table 1 shows the type of case we have used in our study as well as the relative occurrence of thrombosis and embolism in 246 control and 395 treated cases. Patients submitted to sympathectomy and amputation have only recently been treated. They were added because in the year ending July 1, 1950 there was a significant number (5 cases) of emboli in these groups, although the incidence in other relatively minor operative groups remained the same.

We have been criticized in some quarters for discontinuing our control

group, but we believe we are no longer justified in omitting prophylactic therapy in any patient who might develop thrombo-embolism after operation. The last one hundred controls and the first one hundred treated patients were seen simultaneously. The incidence of fatal emboli in patients with a 1:8 level who had no peripheral sign of thrombosis was 2 per cent in our series, which was high enough to make us think that therapy was needed in all instances of possible thrombo-embolism. The risk of Dicumarol is too great to justify its use on surgical wards, particularly on wards where control and accurate following of prothrombin times is impossible. Moreover, even admitting the practicality of the routine use of anticoagulants during the postoperative period, such a group would not serve as a control on the incidence of thrombosis and embolism. It would merely permit comparison with the effectiveness of tocopherol and calcium. Since we know something of the dangers of routine Dicumarol prophylaxis, we did not feel that the use of such a group would add significance to our studies or reduce the overall mortality significantly. For these reasons, we now chose to compile our data in terms of a large group of patients, all of whom receive tocopherol and calcium prophylactically.

Summary

Studies have shown that antithrombic activity of the calcium salt of alpha tocopherol is significant in terms of variations in the level of the prethrombotic index.

A low level (1:8) as measured by the prethrombotic index is associated with a high incidence of thrombosis if, when this level is obtained, the prothrombin time of the patient is at or near normal.

The administration of tocopherol and calcium in prescribed amounts and by prescribed routes is associated with a marked reduction in the incidence of low prethrombotic index levels.

It is conceivable, though not yet proved statistically, that the administration of alpha tocopherol and calcium will reduce the incidence of postoperative phlebothrombosis and pulmonary embolism.

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SAMUEL CLARK HARVEY

A Tribute from a Fellow Surgeon

ALFRED BLALOCK

It is a pleasure to join in this tribute to a great surgeon and teacher, Samuel Clark Harvey. Though not one of his official family, and with no claim of recognition as one of his pupils and associates, nevertheless I share with many others affection as well as admiration for this fine gentleman.

Dr. Harvey's research contributions began when he was a medical student at Yale. It was probably because of these that he obtained an appointment as a house officer at the Peter Bent Brigham Hospital and joined other brilliant young men such as Francis Blake, Elliott Cutler, and Alan Woods, who were working under Dr. Cushing and Dr. Christian in the early days of this hospital. His appointment as Arthur Tracy Cabot Fellow in Surgery is an indication of the impression which he made on Dr. Cushing. The influence of Dr. Cushing is reflected in his publications on neurosurgical problems, but it must be said that these were overshadowed later by contributions to a great variety of problems in surgery. Included among these are papers on wound healing, shock, cancer, burns, abdominal surgery, thoracic surgery, medical history, and medical education. The work on wound healing, probably the most important problem in surgery, is classic.

The rôle which Dr. Harvey has exercised in the training of surgeons approaches in importance the value of his scientific contributions. The careers of those who have trained under him must give him great pride. Great teachers of surgery may use quite different methods in accomplishing their purposes. Dr. Harvey belongs to the group who teaches by example, who stimulates research by his own continuing interest, who exercises care and deliberation on the wards and in the operating room, who stimulates inquiry by avoiding unwarranted dogmatic statements, and who bases his remarks at national surgical meetings on sound experimental and clinical observations.

It is evident to everyone who knows Dr. Harvey that appointments and honors have come to him spontaneously and solely through his own merit. The most recent honor was that of the Presidency of the American Surgical Association. He fulfilled the duties of this office with his usual wisdom and dignity. Sam Harvey's many friends congratulate him on his accomplishments and wish him continued happiness and success in creative work in surgery.

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EVENTS

ALPHA KAPPA KAPPA LECTURE

January 23, 1951

THE GENERAL-ADAPTATION SYNDROME AND DISEASES OF ADAPTATION. By Hans Selye, Professor and Director of the Institute of Experimental Medicine and Surgery, University of Montreal, Montreal, Canada.

In attempting to demonstrate a third specific hormone elaborated by the ovary, extracts of that organ were injected into castrated female rats. Reactions in the injected animals included: (a) hypertrophy and hyperplasia of the adrenal cortices with discharge of their lipid granules; (b) involution of all lymphoid tissues, and blood count changes (lymphopenia, eosinopenia, granulocytic leucocytosis); and (c) ulcerations of the gastrointestinal tract. Extracts of other endocrine organs or body tissue, intended for use as controls, unexpectedly produced the same morphological changes. These observations led to the formulation of the concept of a non-specific bodily reaction to stress situations. All manner of internal and external as well as psychological stresses will produce this non-specific reaction in addition to the specific tissue reaction appropriate to the nature of the stimulus.

The general-adaptation syndrome is conceived as comprising three distinct stages—the alarm reaction, the stage of resistance, and the stage of exhaustion. The latter, resulting from chronic stress after the postulated finite quantity of "adaptability" has been expended, is closely similar in its manifestations to those of physiological senility.

The stress hormones of the adrenal cortex together with their pituitary triggers are thought of as agonists and antagonists. ACTH and cortisone, the gluco-corticoids, are pictured as vying with somatotrophic hormone and DCA, the mineralo-corticoids, for primary effect upon target organs. Experimental support for this characterization is seen in the case of rats which develop a violent arthritis when topical injection of formalin is made. Rats subjected to the same stimulus but which have been conditioned by dosage with ACTH or cortisone do not react with this arthritic change (connective tissue proliferation is thought to be a function of the mineralo-corticoids).

The manifold manifestations of the conditions named as "diseases of adaptation" can be explained by the theory of an identical adaptation syndrome modified in individual diseases by derangements in the hormonal mechanisms, previous diseases of the target organs, diet, heredity, etc. It is hoped that future research will add knowledge, fill gaps, and buttress the conception of the general-adaptation syndrome and that the way will be opened for an additional attack on disease. Thus, therapy will not only be regarded from the viewpoints of etiology and symptomatology but as prevention of the systemic manifestations in the reaction to noxious stimuli.

W. F. S.

TOXICOLOGY SEMINAR

January 26, 1951

CUTANEOUS SENSITIZATION AND CHEMICAL STRUCTURE. By James H. Sterner, Medical Director, Eastman Kodak Co., Rochester, New York.

A vesicular dermatitis occurring in 70% of people involved in colored

film processing prompted an investigation of the development of skin sensitivities of guinea pigs and humans to various chemicals, most of them derivatives of phenol and aniline. All evidence indicates that skin sensitivity is related to circulating antibodies, the chemicals combining with the protein at the site of exposure to form antigens. Pregnancy and inanition appear to depress the sensitization response, while heredity is a contributing factor. No generalization could be made between chemical structure and biologic action. Although increased lipoid solubility parallels skin response to homologues of phenylenediamine, such a generalization does not apply to derivatives of hydroquinone.

J. P. G.

YALE MEDICAL SOCIETY

April 11, 1951

THE PATHOLOGY OF TESCHEN DISEASE. By Dorothy M. Horstmann.

European workers have called attention to supposed similarities between Teschen disease and human poliomyelitis on clinical, epidemiological and pathological grounds. The study reported here took place in Germany in 1949. Inoculations of pigs four to six weeks old and many other animals with various strains of Teschen virus demonstrated that the pig was the only susceptible host. Clinical disease was produced by intracerebral, intranasal, and oral routes, but intramuscular or cutaneous inoculation did not result in overt illness.

The clinical picture of Teschen disease is quite unlike that of human poliomyelitis or experimental poliomyelitis in monkeys. Unlike the limited distribution of the lesions in poliomyelitis, Teschen lesions are widespread throughout the cerebrum and cerebellum, the latter being most heavily infiltrated. Polymorphonuclear leucocytes are rarely seen at any stage in Teschen disease but are fairly common in the inflammatory reaction in the acute phase of poliomyelitis. The neuronal changes in the two diseases are similar. In Teschen disease the lesions tend to form discrete nodules of glialmesenchymal elements, and in this respect it is pathologically far more like Japanese B encephalitis and louping ill than like poliomyelitis.

Studies of physical properties of the Teschen virus indicate a particle size of ten to fifteen mμ. Cross protection, complement fixation, interference, and neutralization tests were performed using a variety of the following viruses: Y-SK and Lansing poliomyelitis, Theiler's TO, GDVII, and FA mouse encephalomyelitis, Eastern and Western equine, St. Louis, Japanese B, louping ill, and Russian Far East encephalitis. The results were uniformly negative. There seems to be no reason for classifying the disease as poliomyelitis-like on the basis of clinical or pathological similarities or antigenic relationships as determined by the methods used.

J. K. R.

A SEQUENTIAL PROCEDURE FOR GRADING MILK BY MICROSCOPIC COUNTS. By M. E. Morgan, P. MacLeod, E. O. Anderson, and C. I. Bliss.

In determining the bacterial count of milk for purposes of grading, the number of fields examined is fixed by regulation. For a microscopic factor of 600,000, thirty fields are examined uniformly for grade A and fifteen fields for approved milk without regard to the relation of the bacterial count to the grade limit. An alternative sequential analysis has been developed in which the size of the count depends upon the number of clumps observed.

Counts on a large number of films showed substantial agreement between the actual distribution of bacteria within a film and that expected by the Poisson distribution for a random arrangement. On this basis the operating characteristic curve for the present inspection plan was determined, showing the percentage of samples now accepted at each true concentration of bacterial clumps. The proposed sequential plan was made to coincide with the present official procedure at 95 to 5 per cent acceptance, its expected operating characteristic curve differing very little from that for the present method over the rest of its range.

The sequential equations have been tested with counts of a hundred fields from more than two hundred. Counts were terminated when twice the present required number of fields had been examined, if a decision was not reached earlier. The operating characteristic curves from these experimental sequential counts agreed with or showed less misgrading than the theoretical curves. The average number of fields needed to reach a decision was largest near the tolerance limit and averaged about 10 per cent greater for grade A milk and 21 per cent greater for approved milk than that predicted from sequential theory. Despite this discrepancy, 36 and 25 per cent fewer fields were required for grade A and for approved milk, respectively, than with the present uniform sample number.

C. I. BLISS

STUDIES ON THE SPREAD AND PREVALENCE OF RHEUMATIC FEVER WITHIN FAMILIES. By Frieda G. Gray.

In studying factors which have influenced the prevalence of rheumatic fever in families observed over a ten- to twenty-year period, poor housing conditions and crowding within the home were found to be significantly greater in the forty rheumatic families than in the thirty control families. Both the rheumatic and control families were of the same income level and of similar sizes. The incidence of common contagious diseases, allergies, non-rheumatic heart disease, and certain other diseases did not differ significantly in the comparable age groups of the rheumatic and control families.

A genetic analysis, suitably corrected for bias of selection and for family size, revealed that the occurrence of the disease approximated the pattern of a single autosomal recessive gene except in the mating of two rheumatic parents. There was no difference in the prevalence of rheumatic fever between the parents or the close relatives of the control and rheumatic families. These facts suggest that heredity, if a factor in the prevalence of rheumatic fever in families, does not follow a specific genetic pattern.

If heredity plays a rôle in the familial prevalence of the disease, it is perhaps one of so-called "inherited susceptibility" or an altered host response to repeated infection which cannot be strictly predicted.

Strict prediction is difficult because the more important factors are repeated beta hemolytic streptococcal infections and poor living conditions, which may allow greater cross infection and a greater number of beta hemolytic streptococcal infections within the family group.

J. K. R.

PHI DELTA EPSILON LECTURE

SOME OBSERVATIONS ON THE ACTION OF MERCURIAL DIURETICS. By Robert F. Pitts, Professor of Physiology, Cornell University School of Medicine, New York, New York.

Mercurial diuretics induce a net loss of water from the body by a direct action on the kidney. The substances act on the distal segment of the tubule to inhibit approximately 15 per cent of the salt absorptive capacity of the tubule. The resultant increased excretion of chloride or sodium or both results in an obligatory loss of water due to the osmotic attraction of the ions. Neither the passive absorption of water from the proximal tubule nor the active absorption of water from the distal tubule is influenced by mercurials. Furthermore, the agents will not block the action of pitressin on promoting water reabsorption in the distal tubule.

Those factors which favor water retention lower the efficacy of the mercurials. Reducing glomerular filtration either by increasing renal arterial pressure or by decreasing renal venous pressure diminishes diuresis, as do low serum chloride levels (relative to bicarbonate) and adrenocortical hyperactivity. Aminophylline, by increasing the glomerular filtration rate, increases the diuretic action of mercurials. The ability of ammonium chloride to potentiate mercurial diuresis may be ascribed to the action of the chloride ion rather than to any acidotic property of the salt, since inhalation of carbon dioxide was without effect on diuresis. Alkalosis, on the other hand, induced by anoxia, and hypercapnia, reduced mercurial diuresis, an action shared by ACTH. Since anoxia is accompanied by a fall in the eosinophile count, ACTH is implicated as the factor reducing diuresis during anoxia, indirectly increasing reabsorption of chloride and, perhaps, sodium.

J. P. G.

ZOOLOGY SEMINAR

April 25, 1951

ANTIMETABOLITES IN THE CAUSATION OF CERTAIN NATURAL PHENOMENA. By D. W. Woolley, Rockefeller Institute for Medical Research, New York.

In living systems, the control of a metabolic process may be exerted through two naturally occurring compounds, chemically very similar, which are antagonists in some enzyme catalyzed reaction. While one of these compounds is generally termed the "essential metabolite" and the other the "antagonist" or "antimetabolite," each may be a true metabolite in its own right, and it may be only in the reactions in which they overlap that they are antagonistic. It is also in these reactions that the relative concentrations of the two compounds are effective in metabolic control.

To illustrate these concepts, the relation between thiamine and pyrithiamine may be cited. (In the latter compound a sulfur-bearing group is replaced by two carbon atoms.) Symptoms of thiamine deficiency are produced in an animal or microörganism when pyrithiamine is fed. If the organism has first been fed thiamine, then, in order to obtain a predetermined deficiency symptom, the amount of pyrithiamine necessary is strictly proportional to the amount of thiamine first fed. This constant ratio between the concentrations of the two compounds is characteristic of competitive inhibition, in which the enzyme being rendered inactive is able to combine with either of the two compounds. It is known in this particular case that thiamine and some constituent of blood can react *in vitro* to produce co-carboxylase; this reaction is blocked by pyrithiamine.

The work to be reported more particularly concerns the antibiotic chloromycetin. This compound is structurally very similar to certain amino acids, especially phenylalanine (PA) and tyrosine. It was determined, using

E. coli, that chloromycetin is an antagonist of PA, but not a competitive inhibitor, for once a critical amount of chloromycetin has been administered, no amount of PA can overcome the effect. It was also shown, using *L. casei,* which is unable to interconvert tyrosine and PA, that PA is much more sensitive to chloromycetin antagonism than is tyrosine.

Chloromycetin differs from PA in four structural features, viz., halogenation, reduction of the carboxyl to a primary alcohol, acylation of the amino group, and the addition of a hydroxyl group in the beta position. All of the possible compounds intermediate in structure between chloromycetin and PA were synthesized and tested for PA antagonism. (By "compounds intermediate in structure" is meant those having the basic PA form with either one, or various combinations of two or three of the alterations characteristic of chloromycetin.) Those compounds having but one structural alteration were inert except for beta-hydroxy PA. Those with two changes were either inert or showed an inhibition which was almost competitive in nature. Of those with three changes, most were active, but none as active as chloromycetin. Chloromycetin appears to be of considerable use to the organism producing it, for it checks the growth of other and possibly competing microörganisms in such a way that they cannot overcome its effect simply by producing more PA.

Another study involved the substances riboflavin and vitamin B12. Each of these has a di-methyl, di-amino benzene structure condensing at the two amino groups. 4,5 di-methyl, 1,2 di-amino benzene is used in the synthesis of these compounds by living organisms. As might be expected, 4,5 di-chloro, 1,2 di-amino benzene inhibits the synthesis of riboflavin and B12, and does so non-competitively. Various analogues were synthesized and tested against 4,5 di-methyl, 1,2 di-amino benzene in riboflavin and vitamin synthesis. Various degrees of effectiveness were found; it seemed that the introduction of halogens and nitro groups into the analogues tended to make the inhibition non-competitive (that is, irreversible).

The full implications of these findings are not yet clear. It may be that the usefulness of chloromycetin lies in the fact that it prevents the incorporation of PA into some essential metabolite, just as pyrithiamine prevents the incorporation of thiamine into co-carboxylase.

R. R. L. G.

OPHTHALMOLOGY SEMINAR

April 27, 1951

IONTOPHORESIS IN OPHTHALMOLOGY. By Gustav Erlanger, New York City.

Iontophoresis, a means of driving ions into tissues by galvanic current, has been utilized in the treatment of several eye disorders. Positively charged ions such as acetylcholine and physostigmine are introduced through the cornea by cathode galvanization, and negatively charged drugs (e.g., penicillin and sulfonamides) by aniontophoresis. In no instance did the current intensity exceed 3 milliamperes. The onset of drug action is said to be more rapid than by subconjunctival injection or topical application. Efficacious treatment of retrobulbar neuritis, acute glaucoma, and corneal ulcers was reported. Zinc ions introduced into the eye by this method stopped bleeding. Barium ions introduced into the eye of the guinea pig produced cataract; none of the other ions tested produced such a response, and no other species examined developed cataract. Iontophoresis was suggested as an effective tool to develop new concepts of the physiology

and pathology of the eye and as an economical method of administering drugs in ocular disorders since the amount of the drug required is exceedingly small.

J. P. G.

YALE MEDICAL SOCIETY

May 9, 1951

NERVOUS CONTROL OF PULMONARY CIRCULATION. By Ivan de Burgh Daly, F.R.S., Director of the Institute of Animal Physiology, Cambridge, England.

Because the concept of nervous control of the pulmovascular bed has, in the past, rested on rather tenuous evidence, several criteria have been formulated which, if met, would seem to provide thoroughly adequate experimental conditions. They are: (i) constant blood inflow to lung, or constant pulmonary arterial pressure; (ii) constant left and right auricular pressures; (iii) constant systemic arterial pressure; and (iv) prevention of bronchiomotor activity.

In order to meet these requirements one must tie off the ventricular halves of both hearts and substitute two separate perfusion systems, one for the greater circulation and one for the lesser circulation. It is necessary to control the greater circulation because the bronchiolar arteries figure in maintenance of pulmonary tissue and changes in their pressure may influence pulmonary arterial pressure.

These conditions satisfied, any changes in vasomotor activity can be followed by changes in pulmonary arterial pressure or blood inflow/outflow ratio. The easy distensibility of the pulmovascular bed tends to minimize pressure changes, but changes in inflow/outflow ratio are larger and, therefore, more sensitive indicators of vasomotor activity.

Stimulation of the middle cervical sympathetic ganglion or of the sympathetic trunk yielded increases in pulmonary arterial pressure up to as much as 3 mm. Hg. Mechanical as well as electrical stimuli were successfully employed. This effect was potentiated by cocaine and could be reproduced with adrenalin, thereby indicating the adrenergic fibers as the active agents.

Microscopic observation of lung in the intact animal revealed that stimulation of the sympathetic trunk, or use of adrenalin, had different effects upon different blood vessels. Some vessels responded with increased rate of flow, others with cessation of flow, and still others with reversal of direction of flow. Consequently, gross observations, such as recording pulmonary arterial pressure or inflow/outflow ratio do no more than indicate the general trend of vasomotor activity.

In view of this and other researches, changes in the pulmovascular bed may be assumed to be mediated in at least three ways: (i) variations in cardiac output, (ii) in gas content of inspired air, or (iii) in sympathetic vasomotor activity.

J. M. Q.

WOODWARD LECTURE

May 14, 1951

STUDIES OF THE THYROID GLAND AS AN EXAMPLE OF MEDICAL RESEARCH. By Sir Charles Harington, Director, H.M. Institute of Medical Research, Hampstead, England.

In the last fifty years of study of the thyroid gland, many branches of the biological and physical sciences have contributed to the present level of knowledge. Discoveries have opened up new pathways of endeavor and fields of investigation. For example, the identification and synthesis of the active thyroid principle, thyroxin, led to the study, testing, and clinical use of the thiourea group of anti-thyroid drugs. Developments in nuclear physics provided a valuable research tool in radio-active iodine. This, in turn, has brought forth new facts concerning the metabolism of iodine, including the concept of thyroid clearance and the demonstration of the remarkable avidity of the thyrotoxic gland for plasma iodide. The mechanism of action of the anti-thyroid drugs has received much attention in the past few years. It now appears that they affect the gland's utilization of iodide by interfering with the oxidizing enzyme system necessary to transform iodide to iodine, a vital step in the halogenation of tyrosine to di-iodotyrosine, the immediate precursor of thyroxin. It has been determined by *in vitro* testing in the speaker's laboratory that there is a spontaneous coupling of the di-iodotyrosine molecules at physiologic pH and temperature to form thyroxin. This would seem to indicate that no enzyme system is necessary in the final step of thyroxin synthesis.

The classical demonstration of the mutual antagonism of the sulfonamide compounds versus para-amino benzoic acid led to a search for structural analogues showing competitive inhibition to thyroxin in the peripheral tissues. Research in this field has been complicated by the fact that most organic iodine analogues show some thyroid-like activity themselves, and where antagonism is noted, it is difficult to determine whether this is a true peripheral effect or is mediated by depression of the anterior pituitary with a lessened output of thyrotrophic hormone.

W. F. S.

BIOCHEMISTRY SEMINAR

May 19, 1951

CHEMICAL STUDIES ON INSULIN. By Albert C. Chibnall, Cambridge University, Cambridge, England.

In view of its relatively small size, insulin would seem to lend itself well to detailed analytical studies of the structure of the protein molecule. It is composed of two or four long peptide chains joined together by disulfide bridges, perpendicular to their long axes. The peptide chains can be separated by oxidation of the disulfide bridges to yield two (or four) peptide chains with cysteic acid residues. These chains have been classified into two groups, A and B. If the molecular weight of insulin is 12,000, it is postulated that there are two type A and two type B chains per molecule.

Extensive studies have been made of the B chain by end-group analysis through use of dinitrofluorobenzene (DNFB) which reacts with the free $-NH_2$ group at one end of the peptide chain to form a derivative. The sequence of amino acids has been determined by digestion with pepsin, trypsin, and chymotrypsin, which are known to attack specific linkages and configurations. The B chain had a postulated molecular weight of 3,338 and contains about thirty amino acids.

Information as to the nature of the A chain is incomplete. If the molecular weight of insulin is 12,000, it is assumed that the two A chains are identical. The author's studies do not lend support to the idea of constant composition of the A chain group.

Two new reagents, lithium-alumino-hydride ($LiAlH_4$) and lithium-boro-hydride ($LiBH_4$), have proved useful in the study of the carboxyl end-groups of the peptide chains and the protein. The question of whether or not amide N appears only in conjunction with glutamic acid and aspartic acid or in conjunction with other amino acids with terminal carboxyl groups has been attacked by Dr. Chibnall. He found that he could account for the amide fraction of the protein as being related to glutamic acid and aspartic acid alone. Some question arises concerning this conclusion because of analytical difficulties involved in the use of the $LiBH_4$ reagent. Attempts to circumvent this difficulty are now being carried out.

The chief advances in this fifteen-year-old research project have been made through the development of the techniques utilizing DNFB, $LiBH_4$, and paper strip chromatography separation of amino acids.

If the molecular weight of insulin is truly 6,000, Dr. Chibnall feels that the synthesis of this protein is well within the range of possibility.

J. M. Q.

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BOOK REVIEWS

PHYSIOLOGY OF SHOCK. By Carl J. Wiggers. New York, The Commonwealth Fund, 1950. xix + 459 pp. $5.00.

This book constitutes an important physiological contribution toward the solution of a complex and ubiquitous clinical problem. Professor Wiggers is primarily motivated to provide a careful analytical study which will increase the understanding and treatment of shock in man. He and his colleagues investigated this subject during the First and Second World Wars, and the present monograph probably constitutes the most complete synthesis available of the many factors involved in shock. The research efforts of the Department of Physiology at the School of Medicine of Western Reserve University were focussed on this problem from July 1940 to September 1946 under the direction of Dr. Wiggers, and of Dr. Harold B. Green who served as co-director for four of these years. Harold Wiggers, David Opdyke, Ewald Selkurt, and Robert Alexander were principal investigators on the project.

Although the book attempts to deal with all problems of the physiology of shock, most of the logical arguments put forward are designed to strengthen the views held by this group and to justify the techniques used by them in their examination of shock. For this reason large sections of the book are devoted to the authors' analysis of their so-called standardized shock. This shock is induced in barbital-anesthetized dogs with usually a small added dose of morphine. The animals are bled from the femoral artery to a low level of mean blood pressure which is sustained for an hour and a half and then exaggerated by further bleeding in order to produce irreversible changes which result in 82 per cent mortality, usually within six hours, even after re-infusion of the total volume of heparinized blood that was withdrawn.

The state of irreversible shock induced by this prolonged hypotension is manifest by a cardiovascular failure which almost inevitably develops beginning an hour or so after re-infusion. This circulatory failure may make its appearance and go on to ultimate fatality even though no significant reduction in blood volume is present. There is a period of compensation following re-infusion during which the blood pressure is maintained at relatively normal values. Although the portal pressure and the effective venous pressure are increased, the heart rate and cardiac output are within normal limits. The basis for increase in portal pressure and effective venous pressure, and the physiological consequences of their appearance are not made entirely clear, but it has been demonstrated that two factors are important in the development of the circulatory failure. There is a peripheral pooling and stagnation of blood in all of the organs, a fact which has been nicely demonstrated by Gibson, *et al.*, and which has been shown to result from failure of the metarteriolar sphincters controlling entry of blood into the capillaries. This capillary stagnation results in a trapping of anywhere from 15 to 50 per cent of the red cells within minute vessels, probably reducing capillary flow by 20 to 40 per cent. In addition to this peripheral circulatory failure due to stagnation, there is definite evidence of myocardial depression. These two factors together account for the failure of circulation even in spite of active support of "shock therapy." Professor Wiggers makes a well-balanced summary of experimental contributions in

regard to the anoxic, toxemic, and neurogenic factors involved in shock, without arbitrarily resolving justifiable differences of opinion about these factors as they are conceived by the investigators whose works he cites. Somewhat neglected by understatement, however, are the evidences of Eversole, Swingle, Wang, and others on the rôle of the nervous system in the dynamic evolution of shock.

Professor Wiggers' superb analysis of the hemodynamic factors, and his very able judgment in interpreting the multiple factors involved in shock, combine to make this a very valuable monograph. He does not hesitate to prescribe suspended judgment on controversial points, and he concludes the monograph with an outline of important channels of research which in his opinion will need to be developed in order to bring an understanding of the physiology of shock to a reasonably complete solution. He makes the important point that clinical practices in reference to the treatment of shock should not be predicated on the idea that a single type of treatment is indicated during all stages of shock. Because this book comes at a time when battle casualties are dying of shock and when the inhabitants of the major cities of the world face the threat of assault by mass destruction weapons, this very provocative volume constitutes a worthy and timely contribution.

ROBERT B. LIVINGSTON

A Classified Bibliography of Gerontology and Geriatics. By Nathan W. Shock. Stanford, California, Stanford University Press, 1951. 599 pp. $15.00.

The introduction very appropriately begins: "The rising interest in gerontology has focused attention on the scarcity of bibliographic and summary material in the field. Since the problems of gerontology extend from the question of changes in enzyme systems within individual cells to important social and economic problems of methods and techniques for the utilization of the capacities of elderly people, practically every scientific and clinical discipline may offer facts and observations of importance. Although some aspects of the field have been summarized and a few special bibliographies have appeared, there is a conspicuous lack of recent comprehensive bibliographic material on the subject of gerontology."

This is a carefully prepared and much needed reference book on the bibliography of gerontology and geriatrics and will be a valuable addition for medical libraries and research workers. There are six main headings: Gerontology; General Orientation; Biology of Aging; Organ Systems; Geriatrics; Psychological Process; Social and Economic Aspects, which in turn are subdivided into two and sometimes three smaller divisions. The main text is followed by a key to *Abbreviations of Journals Cited* of more than 2,300 journals and by indices to authors and subjects.

An excellent feature of this fine bibliography is that provision has been made for publication of supplementary material. Beginning with the April 1950 issue of the *Journal of Gerontology*, additional current material is available under the same major subject headings as in the book. All references appearing after December 1948 have been published in the *Journal*.

In citing periodical literature, the title is given in the original language if it is English, French, German, Italian, Latin, Spanish, or Portuguese. Titles in other languages (Russian, Polish, etc.) are translated into English and are enclosed in parentheses. Where summaries are given in another language, this fact is mentioned. Citations of books follow in the general

form of: author, title of book, publisher, name of the city in which the book was published, date, and pagination.

An inspection of this volume reveals how much material is available on the subject of gerontology.

HENRIETTA PERKINS

PROGRESS IN BIOPHYSICS AND BIOPHYSICAL CHEMISTRY. By J. A. V. Butler and J. T. Randall, Eds. New York, Academic Press, Inc., 1950. viii + 279 pp. $6.80.

This is the first of another "advances" series in the somewhat ill-defined field of biophysics. Generally speaking, the term biophysics includes two fields. One may be described as the application of physical concepts and methods of thought to fundamental biological problems. The other is the application of physical instrumentation to biological problems of any nature —the chief departments being electronic measurements and tracer studies. The editors have happily taken the first to be the true realm of biophysics and have compiled a series of nine papers, one from a Swedish and the remainder from English laboratories.

By the editors' own division the papers may be divided into two categories: first, the physical study of biological molecules, and secondly, the investigation of grosser structure, as nerve and muscle. The first three papers are concerned with properties of solutions of large molecules, macromolecular structure, and the scattering of light and X-rays by solutions of proteins. They are closely written and contain considerable theoretical material.

Three papers deal with instrumentation: phase-microscopy, biological assay with soft X-rays, and local refractrometry. The last is entirely theoretical; it is rather obtusely written and requires considerable physical sophistication.

A rather rambling and heavily documented paper surveys the subject of bioelectric potentials. The mechanical properties of fibers and muscles are related from a thermodynamic point of view to those of plastics and rubber. The most interesting paper from the medical viewpoint is a compilation of data on the tolerance of man for radioactive isotopes. This is the only chapter which requires no physical preparation, and it is a useful reference for types and energies of emitted particles and metabolic fate of the commoner natural and artificial radioisotopes.

Tracer studies are omitted from this collection of the grounds of sufficient coverage elsewhere, as for example, *Advances in Biological and Medical Physics*.

The papers selected for this issue are diverse. It is the professed aim to cover the many topics of biophysics systematically in succeeding volumes. Such treatment will be welcomed by the biophysicist, who must now search for his literature sandwiched in the publications of other disciplines.

W. F. MACN.

ADAPTATION AND ORIGIN IN THE PLANT WORLD: THE RÔLE OF ENVIRONMENT IN EVOLUTION. By Frederic E. Clements, Emmett V. Martin, and Frances L. Long. Waltham, Mass., Chronica Botanica; New York, Stechert-Haffner, 1950. 332 pp. $6.00.

This copiously illustrated volume is based on controlled experiments conducted in the field over a period of some forty years and designed to

determine the rôle of environment in evolution. The first plantings for these experiments were made at Pikes Peak and at Lincoln, Nebraska, in 1901. Under the auspices of the Carnegie Institution of Washington, the program was greatly expanded in 1918 and "three major series of transplant gardens were organized at Pikes Peak, in the Sierra Nevada Mountains and through the Great Plains."

The preface, by Edith S. Clements, states that *Adaptation and Origin in the Plant World* was originally intended to be published in a series of four booklets, and the first in this series (E. V. Martin and F. E. Clements, Carn. Inst. Wash. Publ. 521) was published in 1939. After Dr. Clements' retirement it was planned to publish booklets II and III as one volume. The manuscript for this publication was practically completed before the deaths of Dr. Clements and Dr. Long in 1945. The volume under review consists of most of this material, in addition to some of the information originally intended for booklet IV.

The publication contains numerous tables and graphs and is illustrated by excellent photographs. Although there is considerable information regarding the effect of environment on numerous species of plants, few modern biologists will be converted to the authors' views regarding the rôle of environment in evolution—views which they admit (p. 165) have much in common with those of Lamarck.

It has long been known that organisms show different responses to varying environmental conditions. The authors of this volume conclude that adaptation is brought about by responses to direct physical factors and is expressed both in function and in form. They further state that for all the species employed, there is no evidence that it arises through the selection of genetic strains or variations. They believe that it is possible to convert one Linnaean species into another by altering the environment. Further, that while "the conversion of one genus into another, morphologically at least, is much more difficult than with species, it is far from impossible." In this day of experimental taxonomy and the general acceptance of the genetic definition of species, it is somewhat startling to find the following (p. 166): "The old definition [of species] based upon sterility has long been discarded . . . genetic analysis can be of value taxonomically only in studying differentiation within the species itself."

Experiments along similar lines have been conducted by the research team composed of Clausen, Keck, and Hiesey who approached the problem of species from the standpoints of genetics, cytology, ecology, and geography. Dr. Clausen is a geneticist and cytologist, Dr. Keck a taxonomist, and Dr. Hiesey a physiologist. These authors conclude (Carn. Inst. Wash. Publ. 520, 1940) that natural selection determines the character of the plants that occupy a given environment, and that the ability of a plant to accommodate itself to a new environment is dependent upon its genetic constitution. They further state that, in their studies, changes produced by the environment give no evidence of permanence, and although they may be quite spectacular, they never obscure the individuality of the plant.

The senior author of this volume, Dr. Clements, was one of the pioneers in the field of plant ecology and his reputation as an ecologist is firmly established through his many writings on the subject extending over half a century. It seems unfortunate that this volume, perhaps his last published work, presents many conclusions which will be unacceptable to most students of evolution.

JOHN R. REEDER

THE ATOM AT WORK. By Jacob Sacks. New York, The Ronald Press Company, 1951. xii + 327 pp. $4.00.

Everybody talks about the atom, but few have more than a Sunday supplement knowledge of the simpler aspects of nuclear phenomena. The author, M.D. and Ph.D., and a member of the staff at Brookhaven, treats the story of the atom from its earliest historical conceptions to its possibilities in future war and peace. The style is of the simplest; no previous familiarity with mathematics or physics is required. $E = mc^2$ is virtually the only mathematical expression occurring in the entire work.

The book may be divided into two halves. The first is physical and chemical, dealing with the growth of knowledge of the atom. The chapters on the celebrated works of the Curies, Rutherford, Bohr, Chadwick, Anderson, and others of the pioneers are particularly well done. This historical review includes descriptions of the operation of the various particle-accelerating machines and the chain-reacting pile. The physically oriented may take some offense at the careless use of such terms as force, inertia, and energy, but the sense is usually clear enough.

The second half deals with current tracer techniques, radiation medicine, and briefly with atomic warfare and power. The chapters on tracer techniques may be exasperating at times. Mention is made of useful tools and procedures, without any references to where details may be found.

The author states that the book is intended for the non-scientific reader. As such it is a broad survey; there is no bibliography or documentation of any sort. Still the physicist and biologist may read with profit the sections not pertaining to his own field. The most objectionable features are frequent wordiness and a tone of "talking-down."

The text is liberally supplied with excellent diagrams and half-tones.

W. F. MACN.

RADIOACTIVE TRACERS IN BIOLOGY. (An Introduction to Tracer Methodology). By Martin D. Kamen. 2d ed., revised and enlarged. New York, Academic Press, Inc., 1951. 429 pp. $7.50.

Biologists working with radio-active tracers are already familiar with Martin Kamen's first edition. The second edition offers two special points of interest. In the first place, it constitutes Volume I of a projected series of monographs on organic and biological chemistry to be edited by Louis F. Fieser and Mary Fieser. In the second place, extensive revisions of several chapters and appropriate additions to the text have brought the original monograph abreast of recent developments in a rapidly advancing field. For instance, a chapter on radiation hazards and dosage has been included, which will give newcomers assurance as to their own personal safety.

This monograph is not designed for highly restricted specialists. Rather, it has been prepared for biologists (physiologists, biochemists, and clinical investigators) who need a sound background in the principles and pitfalls of tracer techniques. There are 429 pages, including the index, comprising 14 chapters and a technical appendix with general bibliography. The early chapters discuss the nature of isotopes, their characteristic radiations, and methods for quantitative detection. Tracer methodology is explained both from the biochemical and the physiological (or medical) standpoint. Individual chapters describe the properties and application of commonly used isotopes, viz., tritium (H^3), carbon (C^{11} and C^{14}), phosphorus (P^{32}), sulfur (S^{35}), alkali metal and alkaline-earth tracers, and halogen tracers.

Finally, special uses of biologically important isotopes are described for manganese, iron, cobalt, copper, zinc, molybdenum, arsenic, selenium, gold, and other metals.

The text is clearly written, and illustrated with frequent diagrams and tables. There are abundant references; and a substantial amount of simple mathematics is included. In any laboratory where graduate students, research fellows, or skilled technicians work, this handy monograph will prove indispensable.

WILLIAM T. SALTER

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